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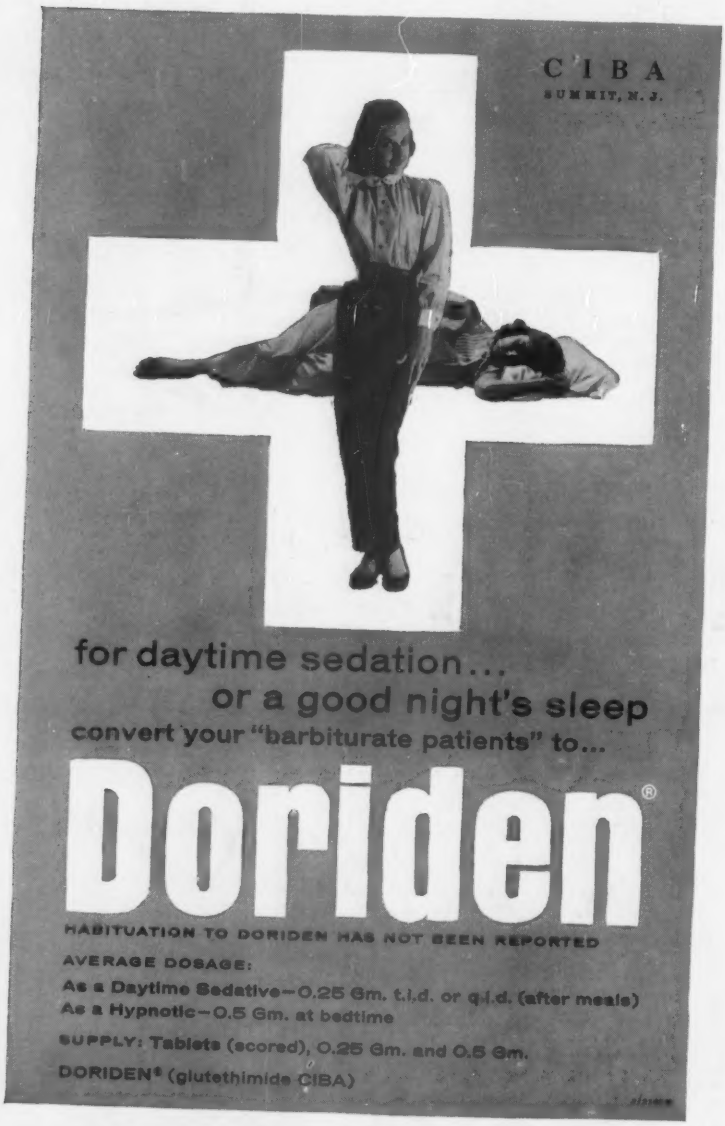
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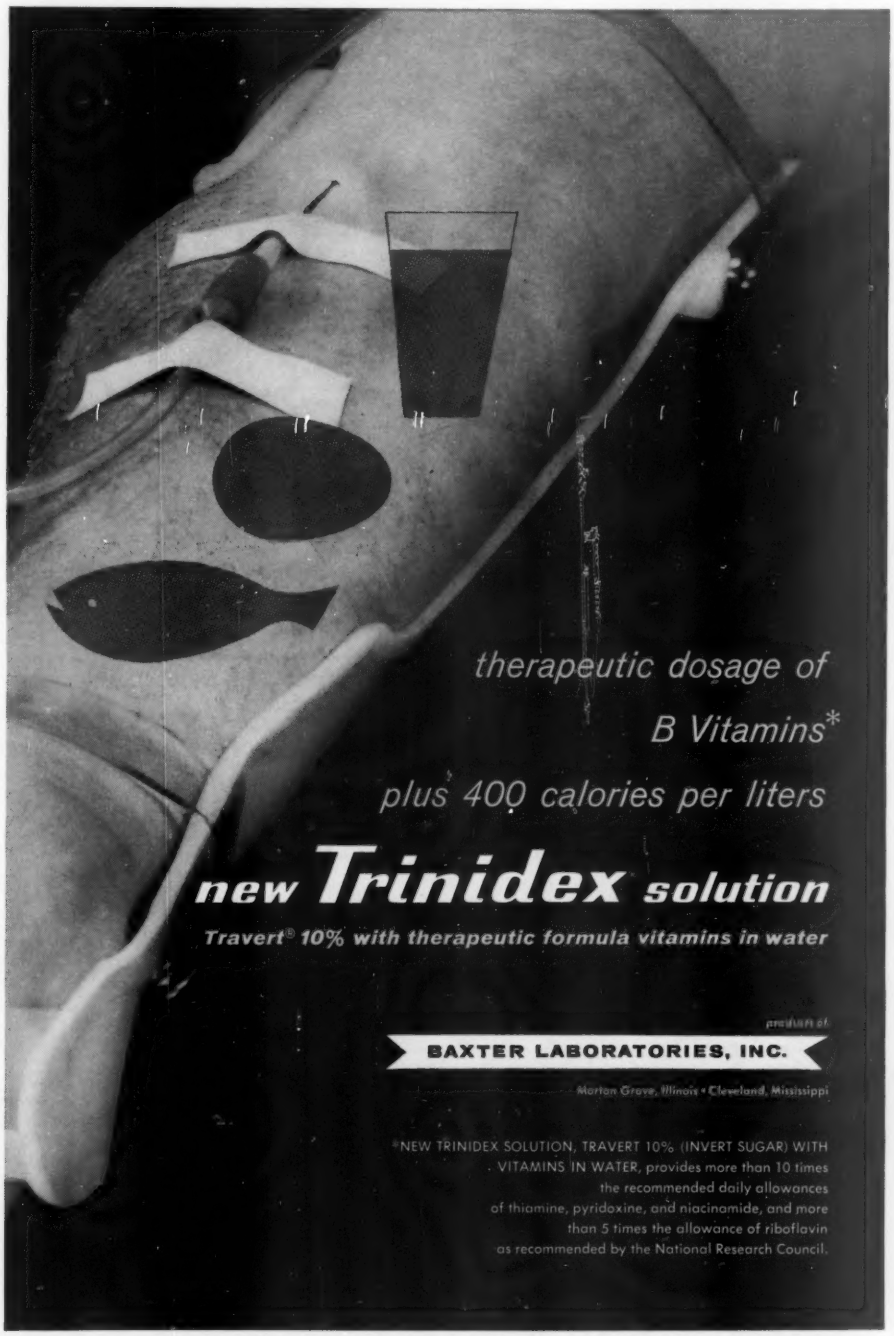
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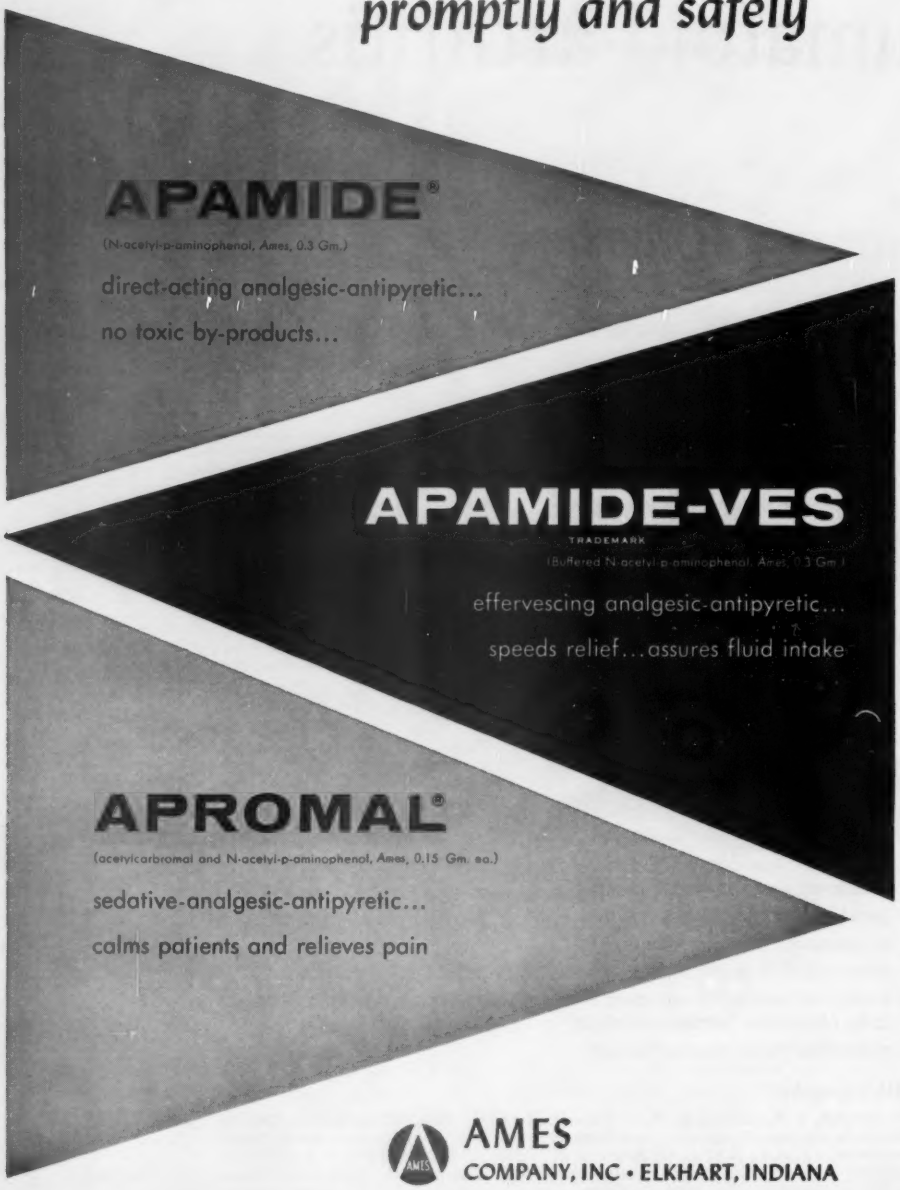

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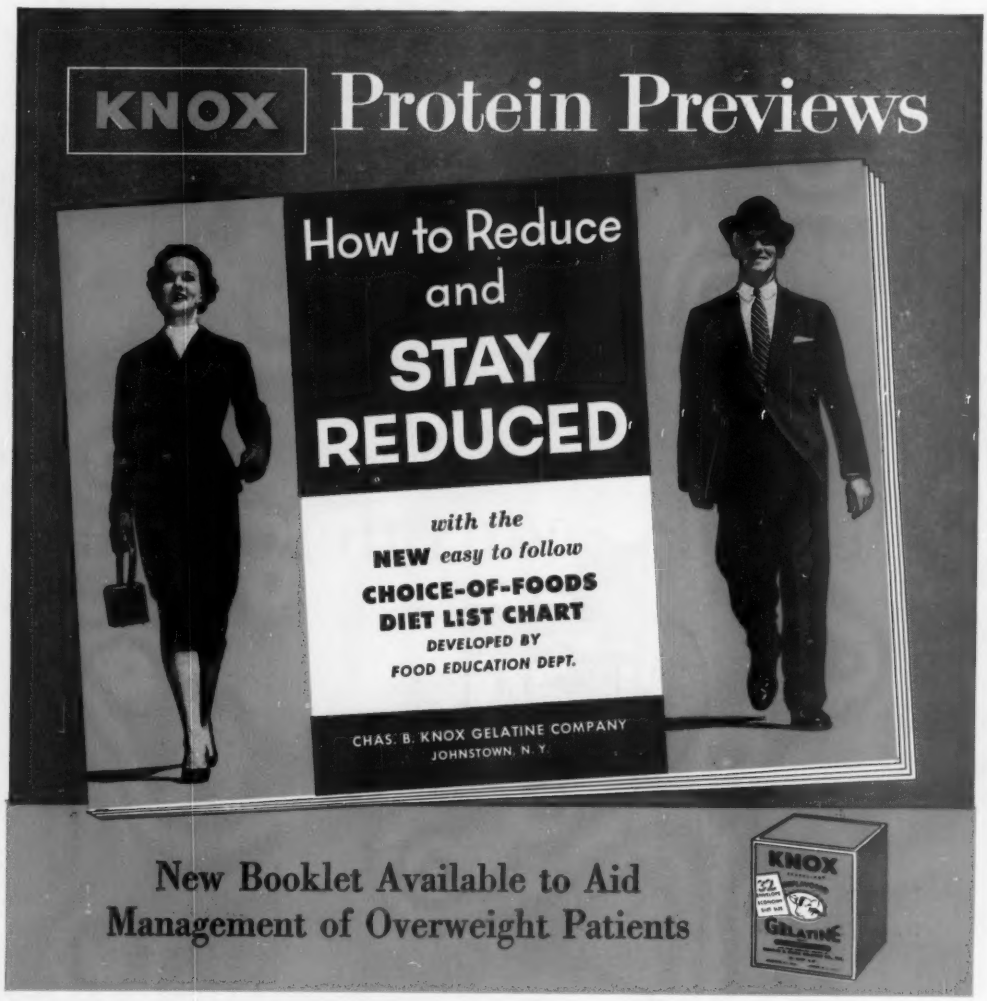

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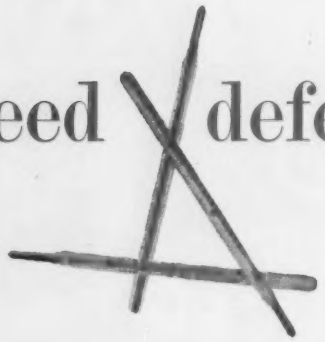

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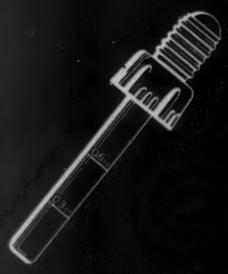

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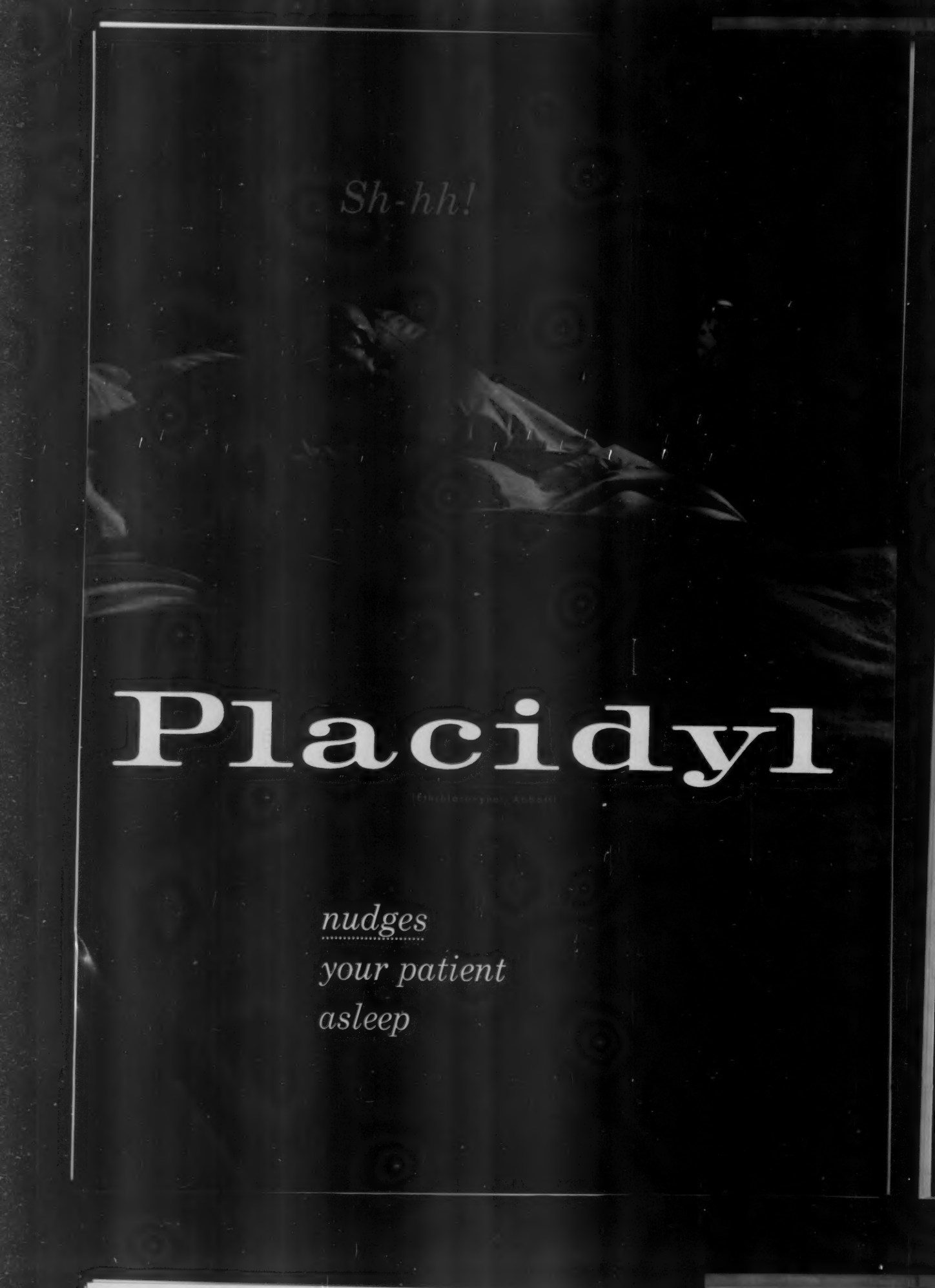
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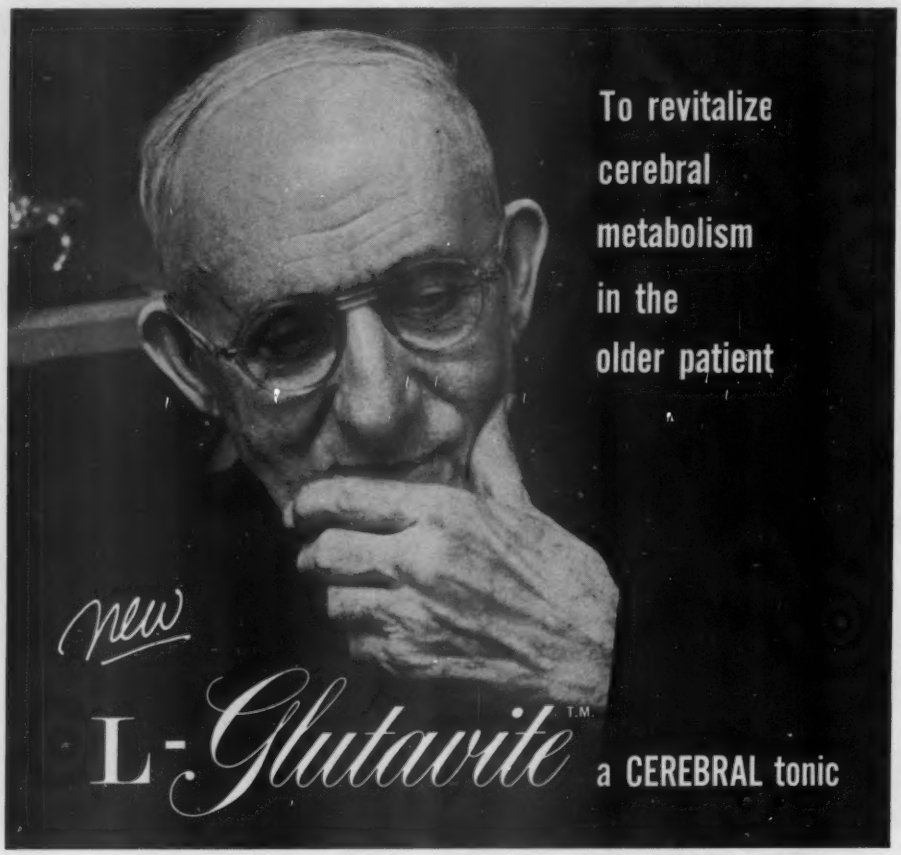

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1. Himwich H.E.: Paper presented at American Psychiatric Association meeting, St. Louis, May, 1954.
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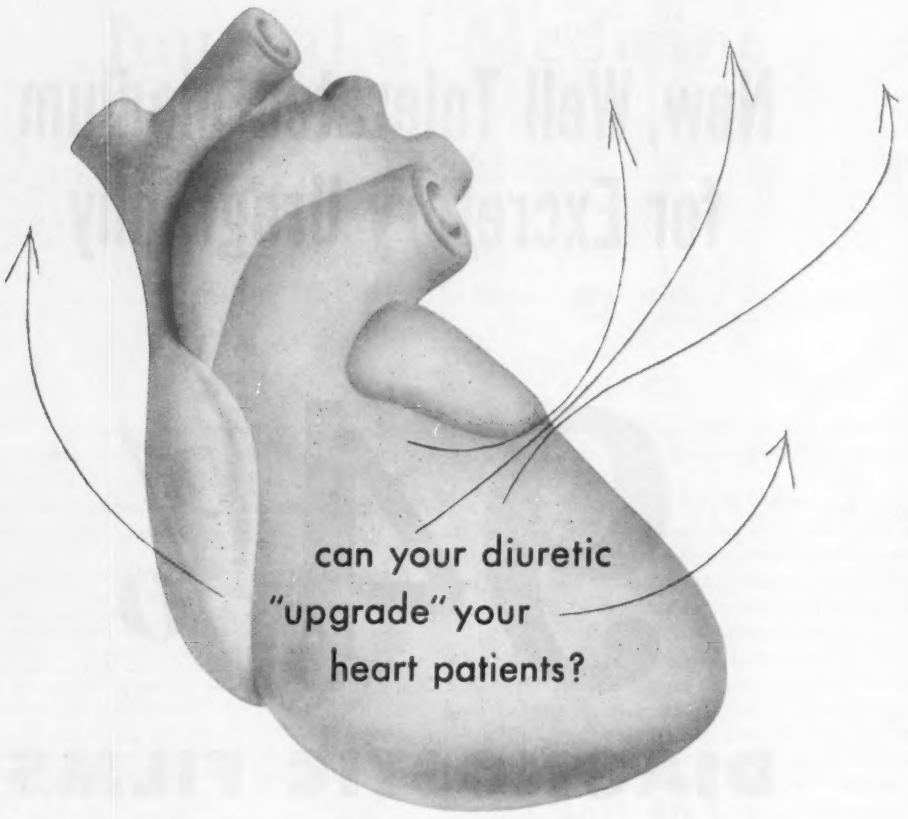

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Volume 253 OCTOBER 6, 1955 Number 14

PHLEBITIS

A Study of 748 Cases at the Boston City Hospital

JOHN J. BYRNE, M.D.*

BOSTON

THERE is a growing impression in the medical profession that division of the proximal veins is of doubtful value in the prevention of pulmonary embolism. In recent reviews of this problem the following statements have been made:

> During the past two decades there has been considerable revival of interest in this procedure as a therapeutic measure with some workers strongly advocating its prophylactic value, particularly in patients with thrombophilic tendencies. More recently, however, there has been a growing evidence of its dubious value suggesting that now after an interval of several decades the second cycle in the status of this procedure is about to be completed.[1]

> Therefore, ligation was found not to be a preventive measure of choice except where it was desirable to eliminate varicose veins, a common site for recurrent thrombophlebitis with secondary emboli.[2]

> The use of vein ligation as a prophylaxis for pulmonary embolism has distinctly decreased in favor during the last few years.[3]

This impression is so contrary to experience at the Boston City Hospital that a study was made of 748 patients with phlebitis admitted to this hospital over the past decade. Only cases in which definite or highly suspicious leg signs preceded pulmonary embolism were studied. This series does not include any cases in which a fatal pulmonary embolism took place in the absence of leg signs. The deaths listed were due to definite or probable pulmonary emboli.

VITAL STATISTICS

The age distribution in this series is presented in Figure 1. The age group from fifty to seventy-nine years exhibited the greatest frequency of phlebitis. Eighty-three per cent of the cases occurred in patients over the age of forty. This figure coincides with most of the other large series reported in the literature.[4-10] This increased frequency of phlebitis in the older age group is explained by the greater number of predisposing diseases in this segment of the population. However, phlebitis may occur at any age, and 9 cases were discovered before the age of twenty.

The mortality for the various age groups is shown in Table 1. There was an increased rate with each decade up to fifty, when the mortality rate remained fairly constant. This probably mirrors the increased frequency of cardiac disease in the older age groups.[9]

The sex distribution was approximately even, 52 per cent of cases occurring in males and 48 per cent in females. In the younger decades phlebitis occurred more frequently in females, probably reflecting obstetric complications. In the middle years the male percentage rose, probably because of the increased occurrence of coronary-artery disease. During the later years the ratio was fairly even, a slight emphasis on the women being due to their longevity (Fig. 1). The over-all mortality for both groups was about the same: 19 per cent for female and 23 per cent for male patients.

The incidence of phlebitis during the ten-year study at the hospital appeared to increase annually. For example, in 1943, it was approximately 1.3 per 1000 admissions, rising to 3.9 per 1000 admissions in 1951. A variation over this period could not be ascertained owing to a breakdown of the record system in two of the post-war years. This increased incidence is probably due to a keener awareness of the problem by the house staff, but an increasing geriatric population may also be a factor.

No seasonal variation of the disease could be found (Table 2). This contradicts a widespread conception that there is an increased occurrence of phlebitis during the fall and winter.[10,11] However, many other investigators have found no relation to season.[12,13]

PREDISPOSING DISEASES

The various conditions predisposing to phlebitis are listed in Table 3, which shows the frequency of each condition, together with the results of the various methods of treatment for each.

*Associate professor of surgery, Boston University School of Medicine; director, Third (Boston University) Surgical Service, Boston City Hospital.

Cardiac Disease

Cardiac disease was the most significant predisposing factor in this series (28 per cent). This compares with similar analysis made by other investigators: 68 per cent,[6] 50 per cent,[7] 13.15 per cent,[12] 80 per cent[13] and 52 per cent.[14]

The ominous significance of cardiac disease is further emphasized by the fact that 38 of the remaining 77 fatal cases were associated with heart disease. In other words heart disease was present with 73 per cent of the fatal pulmonary emboli.

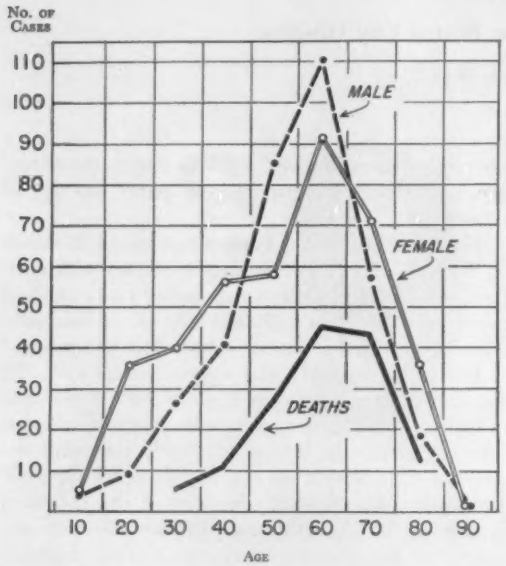

FIGURE 1. *Age and Sex Distribution in 748 Cases of Phlebitis, together with Age Distribution in 145 Fatal Pulmonary Emboli.*

The chief factor in producing phlebitis in cardiac patients is probably venous stasis. Paterson and McLachlin[15] have recently found that if thrombi are examined in their early stages before they completely occlude the lumen of the vein they can be seen to originate in the locations where stagnation of blood should be maximal — in the cul-de-sacs formed by valve pockets. However, it is well known that stasis alone will not experimentally produce thrombosis.[18-21] Hypoxic damage to the venous endothelium has been suggested by O'Neil[22] as an additional cause. There is still the possibility, mentioned by Rosenthal,[13] that some change in the circulating blood in cardiac patients accounts for the thrombosis. Dehydration produced by diuretics is occasionally involved.

Postoperative Cases

One hundred and seventy-four cases of phlebitis occurred during the postoperative period (23 per cent of the entire series).

Associated heart disease was present in 68 cases, 14 of which were fatal.

Associated carcinoma was present in 38 cases, and the sites were as follows: colon, 18 cases; stomach, 5 cases; prostate, 3 cases; ovary, 3 cases; pancreas, 2 cases; and bladder, lung, brain, penis, breast, tonsil and kidney, 1 apiece.

The type of operation varied widely (Table 4).

The reasons for postoperative phlebitis may be varied, as follows: *venous stasis* due to cardiac disease, vasospasm, tight abdominal binders, shallow pulmonary ventilation, abdominal distention, insufficient ambulation or shock; *changes in the intima* produced by the aging process or by trauma during the operative period; or *increased coagulability* of the blood secondary to dehydration, anemia, infection, necrosis and carcinoma. The coagulation defects in the postoperative period were recently summarized by Warren[23] as follows:

> In general . . . the postoperative period seems to be divided into two parts, the early and the late, each one occupying approximately a week. During the early period a decrease in prothrombin conversion accelerators and a thrombocytopenia occur; on the other hand the coagulation time of whole blood, whether in glass or silicone or whether with added heparin, is shortened, antithrombin activity is decreased, and prothrombin consumption is increased. During the later postoperative period the prothrombin conversion accelerators return slowly to normal, thrombocytosis occurs, prothrombin consumption and antithrombin return to normal, and fibrinogen, which has begun to rise in the mid-early period, remains elevated until the ninth or tenth day, when it also returns to normal.

TABLE 1. *Relation of Age and Mortality from Pulmonary Emboli in 748 Cases of Phlebitis.*

Age	Mortality
decade	%
10	—
20	2
30	9
40	11
50	29
60	24
70	34
80	22
90	—

TABLE 2. *Seasonal Distribution of 748 Cases of Phlebitis.*

Season	Percentage
Winter	26
Spring	24
Summer	24
Fall	26

Trauma

Eighty-four cases followed trauma to the lower extremity (11 per cent of the entire group). Thirty-two patients had associated heart disease, with 2 deaths. The most common trauma was fracture of the femur (35 cases).

The cause of thrombosis is obvious with local trauma, since practically all experimental investigators have demonstrated that such trauma could damage the endothelium.[19-22] Moreover, trauma at a distance may alter the coagulability of the blood, as suggested by Ochsner and DeBakey.[24] However, immobilization of the traumatized extremity may be an even more important factor.

Idiopathic

Forty-nine patients appeared to have no predisposing disease whatsoever (6.5 per cent of the entire group). The percentage in this study with spontaneous or idiopathic phlebitis may be compared to that in other series — that is, 4.5 per cent,[25] 17.5 per cent[20] and 27.1 per cent,[26] the last (and high) rate being found in a series of young men.

The cause of phlebitis in this group could be related to minor trauma or effort. Crane,[27] in a review of 23 cases culled from his own private practice and from the literature in which there seemed to be some relation to effort or strain, stated that either produced a marked increase in venous pressure that might damage a vein wall or valve and precipitate thrombosis, particularly if it was associated with muscular contractions of the limb and peripheral venous engorgement.

Naide described 6 tall patients in whom spontaneous venous thrombosis occurred after strain of one type or another.[28] In 3 of these pulmonary infarction was the first symptom; in the others anticoagulants did not prevent embolism, and division of the iliac or femoral veins was necessary.

Infection

Forty-seven cases of phlebitis (6.3 per cent) were secondary to infection. The most common infection was pneumonia (20 cases), tuberculosis being a close second (14 cases). The remainder were leg cellulitis, infections of the upper respiratory tract, septicemia, abscess, pyelonephritis and meningitis. The fact that only 14 cases of phlebitis were found in people with tuberculosis is of interest, since tuberculosis is fairly common in this hospital. Only 1 of these patients had a fatal pulmonary embolism. These facts are in agreement with findings from other institutions.[1]

Since John Hunter,[29] in 1794, described the vascular changes in phlebitis as a result of infection, many investigators have implicated this as a cause of

TABLE 4. *Operations Predisposing to Phlebitis.*

OPERATION	NO. OF CASES
Hip nailing	28
Genitourinary surgery	16
Gynecologic surgery	15
Appendectomy	14
Colectomy	13
Hernia	12
Biliary surgery	13
Gastrectomy	13
Exploratory laparotomy	10
Miscellaneous	40
Total	174

TABLE 3. *Conditions Predisposing to Phlebitis.*

CONDITION	PERCENTAGE OF ALL CASES	NO TREATMENT			SURGICAL VENOUS DIVISION			ANTICOAGULANT THERAPY			TOTAL NO. OF CASES	TOTAL NO. OF DEATHS	AVERAGE MORTALITY*
		NO. OF CASES	NO. OF DEATHS	MORTALITY*	NO. OF CASES	NO. OF DEATHS	MORTALITY*	NO. OF CASES	NO. OF DEATHS	MORTALITY*			
				%			%			%			
Cardiac disease	28.0	126	60	47	80	3	3.7	10	5	50	216	68	31
Postoperative complication	23.0	47	23	48	123	4	3.2	4	0	—	174	27	15
Trauma	11.0	29	5	17	52	1	2.0	3	0	—	84	6	7
None (idiopathic)	6.5	23	1	4	23	0	—	3	1	33	49	2	4
Infection	6.3	23	2	8	19	0	—	5	0	—	47	2	4
Varicose veins	5.4	24	4	16	16	0	—	1	0	—	41	4	9
Childbirth	5.4	19	1	—	20	0	—	2	0	—	41	1	2
Hemiplegia	5.0	24	18	75	11	0	—	3	3	—	38	21	55
Cancer	3.7	18	11	61	10	0	—	0	0	—	28	11	39
Miscellaneous	4.0	14	3	21	15	0	—	1	0	—	30	3	10

*From pulmonary embolism.

the disease. Barker et al.[13] found it to be a predisposing condition for phlebitis in 22 per cent of a series of 1665 cases of postoperative thrombophlebitis. They also reported that venous thrombosis was about twice as frequent in pulmonary embolism after appendectomy for ruptured appendix as in that after appendectomy for chronic or subacute appendicitis.[30]

In the laboratory animal, when local infection is added to stasis and venous damage, thrombosis develops.[20] However, infection anywhere in the body may predispose to phlebitis. Dietrich[31a-c] believed that infection directly sensitized the endothelium, after which there was a direct reaction between the endothelium and the blood to form a thrombus. Jürgens,[32] by the use of a capillary thrombometer, found a decrease in clotting time in infections. However, the changes in blood coagulation observed in infection are not clearly understood.

A great epidemic of thrombophlebitis was seen in East Africa by Manson-Bahr and Charters.[33] There was usually a relative lymphocytosis, with negative bacteriologic findings, and an epidemiologic relation to infectious hepatitis that was so close as to suggest that the syndrome might be caused by a virus transmitted chiefly by needle puncture, since most of the patients had received a previous venepuncture for neoarsphenamine therapy or artificial pyrotherapy with typhoid-paratyphoid vaccine or diagnostic purposes.

Varicose Veins

Thirty-one patients had varicose veins as prominent factors in their history (5.4 per cent of series). Three of these had associated heart disease. The cause of the phlebitis in these cases was probably venous stasis.

Obstetric Factors

Forty-one obstetric cases were observed (5.4 per cent of group). The phlebitis is probably associated with venous stasis since Wright et al.[34] have shown that there is a marked slowing of the blood flow during the last trimester of pregnancy, particularly during the time of labor. The low mortality is similar to that reported throughout the literature.[1] This may be due to the younger age of this group of patients.

Hemiplegia

Thirty-eight cases were associated with hemiplegias and, as was expected, there was a high mortality (55 per cent). Twenty-five patients had associated heart disease, and among this group there were 15 fatal cases.

Most authors list hemiplegia under the cardiovascular causes of phlebitis, but I prefer to keep it in a separate classification to remind physicians who are treating patients with hemiplegia of the possibilities of this dangerous complication.

In a previous study devoted to 130 fatal emboli proved at autopsy the hemiplegic group was the third most common group.[8] It is of interest that the hemiplegia was improving in some degree in the majority of cases, and the prevention of the fatal pulmonary embolism would have prolonged many lives. In none of the cases was pulmonary embolism even thought of clinically as a cause of death.

Cancer

In 28 cases cancer was the sole predisposing factor (3.7 per cent). However, if the 38 patients who were operated on are added to this group cancer becomes a predisposing factor in 8.8 per cent of the entire series. These figures compare with those in other series in the literature: 32 per cent,[6] 21 per cent[7] and 24.9 per cent.[12]

The sites of the carcinomas in the entire series were as follows: colon, 24 cases; stomach, 12 cases; breast, 6 cases; ovary, 4 cases; cervix, 3 cases; prostate, 3 cases; lung, 2 cases; pancreas, 2 cases; uterus, 2 cases; and miscellaneous locations, 8 cases.

Eight patients had associated heart disease, and 7 deaths occurred in this group.

The relation of carcinoma to phlebitis has been known for many years, since Trousseau's[35] description in 1868. Hubay and Holden[36] recently reviewed much of the literature on this subject and presented 7 cases of their own. They suggest that the common denominator for peripheral venous thrombosis and neoplasia may be the presence of necrotic tissue in the carcinoma. Lawrence et al.[37] have demonstrated a thromboplastic property of transplantable V_2 carcinoma in rabbits.

Miscellaneous Conditions

Thirty cases made up this group (4 per cent of the entire series), comprising such conditions as gastrointestinal hemorrhage, ulcerative colitis, peptic ulcer, nephritis, biliary-tract disease, senile dementia, ruptured intervertebral disk, cirrhosis and myelitis. In practically every case the patient was confined to bed.

Relation of Clinical Manifestations to Mortality

The terms "phlebothrombosis" and "thrombophlebitis" are applied to various stages of phlebitis, as if they were two separate conditions:

> In thrombophlebitis the clinical manifestations both locally and systemically are pronounced and impressive, there being considerable swelling, pain and discoloration in the extremities and constitutional manifestations of fever, tachycardia and leukocytosis . . . On the other hand, in phlebothrombosis, there are few or no local manifestations in most cases and only moderate degrees of tenderness, pain and swelling in some cases . . . Per-

haps the most important contrasting feature with thrombophlebitis and phlebothrombosis is the fact that in the former pulmonary embolism occurs rather infrequently; whereas in the latter, there is a great likelihood of pulmonary infarction or embolism . . . The fact remains, however, that these characteristics in contrasting clinical patterns of the disease occur with sufficient regularity to make them readily distinguishable.[1]

The low rate of occurrence of fatal pulmonary embolism in thrombophlebitis was further emphasized in the series of Barker et al.,[12,30] in which it occurred in 6.6 per cent of 273 cases of iliofemoral thrombophlebitis.

It has been my impression that — aside from the rare cases of septic or suppurative thrombophlebitis — all phlebitis is essentially the same process but with varying manifestations. Consideration of the process as two separate conditions — that is, phlebothrombosis and thrombophlebitis — gives a false sense of security when one is dealing with this disease.

The conservatively treated cases seen at this hospital were classified according to the severity of the clinical manifestation, as follows:

Grade 1. Minimal calf tenderness or edema.
Grade 2. Moderate to severe calf edema or tenderness or both.
Grade 3. Thigh tenderness, with no edema.
Grade 4. Thigh tenderness, with edema.
Grade 5. Bilateral phlebitis.

In the bilateral group the limbs were not graded individually. The clinical manifestations were then correlated with the deaths (Table 5).

Grade 1 phlebitis, which in most series is represented as phlebothrombosis, was associated with a 53 per cent mortality. Although Grade 3 and 4 phlebitis, which are classified as thrombophlebitis or iliofemoral thrombophlebitis by other authors, present a lower mortality (29 to 31 per cent), there is little to reassure a physician that no pulmonary embolism will occur. It is true that the embolism in these cases usually comes from the contralateral leg, but the patients should be treated with as much vigor as those with phlebothrombosis.

In the entire series the left leg was involved in 356, and the right in 247 cases, with bilateral involvement in 145. This preponderance of the left leg over the right has been noted in most series, but the reason for it is not clear.[38]

Valves in the iliac and common femoral veins are more often absent on the left.[39,40] If one believes that the main function of valves is to protect capillaries and venules from sudden excessive rises of blood pressure during muscular exercise, the relative absence of valves in the left leg could predispose this leg to more trauma from such sources as straining, giving a greater opportunity for areas of thrombosis to develop.[41-43]

Obstructions were found at the mouth of the left common iliac vein in 23.8 per cent of 399 veins examined by Ehrich and Krumbhaar,[44] confirming a previous study by McMurrich.[45] The obstructions were of five general types. Group 1 showed all transitions from "a narrow thickening" to triangularly shaped areas obstructing the upper pole of the mouth. Patients with Group 2 obstruction presented the same picture except that all had a channel passing along the left wall of the vein. Group 3 included several varieties of adhesions dividing the lumen into two more or less equal portions. Group 4 comprised adhesions at the lower pole of the mouth showing a tendency to extend behind the valve, and Group 5 miscellaneous lesions, most of which were characterized by multiple irregular bands. These lesions were all in the left common iliac vein and may have been produced by the constant pressure of the right iliac artery. It is conceivable that this pressure interferes with the proper development of the orifice or causes an injury, resulting in organization and fibrosis. These authors had 1 case of adhesion in the right common iliac vein, but this was associated with situs inversus of the lower vena cava.

TABLE 5. *Relation of Fatal Pulmonary Emboli to Clinical Manifestations of Phlebitis.*

CLINICAL MANIFESTATIONS	NO. OF CASES	NO. OF DEATHS	MORTALITY
			%
Grade 1	43	23	53
Grade 2	146	20	27
Grade 3	60	19	31
Grade 4	28	8	29
Grade 5	70	38	55

RELATION OF THERAPY TO MORTALITY

Three hundred and forty-seven patients received conservative therapy, with 128 deaths (37 per cent). This high mortality reflects the great number of cardiac cases in the series. However, it probably represents an average figure since, as Wright and Foley[2] state, "Once thrombophlebitis has been recognized in the absence of anticoagulant therapy, the risk of pulmonary embolism ranges from 4 to 60 per cent."

Three hundred and sixty-nine patients received surgical therapy, with 8 deaths (2.1 per cent). In 7 of the surgical cases primary division of the vena cava was performed; in the remainder bilateral femoral-vein division was carried out.

The surgical cases were further studied for adherence of the clot in the femoral vein at the time of surgery (Table 6). In 273 cases no clot was found; there was 1 death, which occurred in a seventy-two-year-old man with decompensated arteriosclerotic

heart disease and bronchiectasis. A swollen and tender left calf developed while he was in the hospital, and a bilateral division of the superficial femoral veins was done. He did poorly after this and died a week later. Permission for autopsy was not obtained; therefore, one cannot be sure whether this was a myocardial infarction, cardiac failure or pulmonary embolism.

In 66 cases a clot found at the time of surgery was easily removed, a good retrograde flow of blood being obtained. The single death in this group occurred in an eighty-one-year-old woman with arteriosclerotic heart disease who entered the hospital with an intertrochanteric fracture of the left hip, for which hip nailing was done. Five days later, tenderness in the left calf developed, and a bilateral division of the superficial femoral veins was done. A free clot was found and removed by suction. She did well for approximately a week when, while on crutches on the ward, she suddenly became weak and faint and died. Post-mortem examination revealed a massive blood clot in the pulmonary artery and another clot in the left vena profunda femoris extending into the iliac vein.

TABLE 6. *Relation of Fatal Pulmonary Emboli to Adherence of Thrombus at the Time of Surgery.*

STATUS OF THROMBUS	NO. OF CASES	NO. OF DEATHS	MORTALITY
			%
No clot	273	1	0.37
Clot easily removed	66	1	1.5
Clot adherent (no further therapy)	18	6	33.0
Clot adherent (anticoagulants or vena-cava division)	5	0	——

In retrospect, the common femoral vein should probably have been divided. The clot was probably present in the vena profunda at the time of surgery, especially since the predisposing disease was hip trauma. It appears that whenever the thigh veins are involved clinically or at operation, the common femoral vein should be divided.[8,46a]

In 23 cases the clot was difficult to remove at operation, and a free retrograde flow of blood was unobtainable. In 18 of these cases nothing further was done, and 6 patients died. Four were treated subsequently with anticoagulants, with no deaths. In another case the vena cava was divided shortly after the femoral division, with a successful outcome.

These figures clearly demonstrate that when a clot is found and is not easily removed the patient should be given additional therapy in the form of anticoagulants or vena-cava division.

Thirty-two patients were treated with anticoagulants alone, and 9 died (29 per cent). Two died within twenty-four hours of the beginning of anticoagulant therapy and before satisfactory blood levels could be obtained. Two patients threw off a massive embolism approximately three weeks after the cessation of anticoagulant therapy. Although many authors would not include these 2 cases as failures of anticoagulant therapy they represent two of the problems posed by this type of treatment: How soon can one get protection; and how long must the protection be maintained before the anticoagulant treatment is stopped? The remaining 5 patients appeared to be on adequate anticoagulant therapy, with the prothrombin time at approximately 30 per cent or the clotting time above thirty minutes.

Eight of the patients treated by surgery had been on anticoagulant therapy, and emboli had taken place before operation. There were 4 cases of hemorrhage in patients who were undergoing anticoagulant therapy: 1 severe gastrointestinal hemorrhage, 1 subcutaneous hemorrhage, with subsequent slough of a large area of skin, 1 cerebrovascular hemorrhage, and 1 fatal massive retroperitoneal hemorrhage at the site of a lumbar block in a patient with very severe cardiac disease.

Because of the disparity in the number of cases in each group it is difficult to compare the surgically treated with the anticoagulant-treated patients. However, there appears to be no obvious difference between the two groups in the two most important factors: age and cardiac disease. The frequency of patients over the age of forty was similar in the anticoagulant-treated group (84 per cent) and in the entire series (83 per cent). Among 18 anticoagulant-treated patients with primary or associated cardiac disease there were 8 deaths (mortality of 44 per cent); the corresponding mortality among the surgically treated patients with primary cardiac disease was 3.7 per cent. It thus appears that the patients treated surgically in this hospital fared better than those treated with anticoagulants.

TABLE 7. *Relation of Postphlebitic Syndrome to Therapy.*

THERAPY	NO. OF CASES	POSTPHLEBITIC SYNDROME
		%
Surgery	67	46
None	39	84
Anticoagulants	3	66
Total	109	
Average		49

RELATION OF PREMONITORY PULMONARY EMBOLI TO MORTALITY

Some authors maintain that there is no need for treatment of phlebitis unless an embolism has occurred. This is certainly far from the truth. In this series of 144 cases of fatal pulmonary emboli in pa-

tients with pre-existing phlebitis the first embolus was fatal in 122 cases (84 per cent). Only 22 patients (16 per cent) had premonitory emboli. These figures are slightly lower than those of Barker et al.,[47] who found that 36 per cent of the fatal emboli were preceded by one or more episodes of nonfatal embolism.

Relation of Therapy to Postphlebitic Syndrome

One hundred and nine patients in this series returned to the hospital one to five years after the primary therapy for phlebitis. Sixty-seven were treated by surgery, and in 46 per cent the postphlebitic syndrome developed. In 87 per cent of 39 who received no treatment, the postphlebitic syndrome developed. Three were treated with anticoagulant therapy, the postphlebitic syndrome occurring in 2 (Table 7).

Table 8. *Relation of Postphlebitic Syndrome to Clinical Manifestations of Phlebitis.*

Clinical Manifestation	No. of Cases	Postphlebitic Syndrome
		%
Grades 1 & 2	87	36
Grades 3 & 4	41	80

Study of the occurrence of the postphlebitic syndrome from the point of view of clinical severity demonstrated that 87 cases were Grade 1 or 2 phlebitis, and in 36 per cent of these the postphlebitic syndrome developed. In 41 cases phlebitis extended into the thigh, and in 80 per cent of these the postphlebitic syndrome occurred (Table 8).

These two studies suggest that the postphlebitic syndrome is due not to the type of therapy but to the clinical severity of the phlebitis.

Summary and Conclusions

Seven hundred and forty-eight cases of phlebitis seen at the Boston City Hospital over the past decade are reviewed. Eighty-three per cent of the patients were over forty years of age; the mortality increased with age. No seasonal variation could be found.

The predisposing conditions in order of frequency were cardiac disease, postoperative state, trauma, idiopathic manifestation, infection, varicose veins, childbirth, hemiplegia, cancer and miscellaneous.

Fatal pulmonary emboli occurred frequently in phlebothrombosis and thrombophlebitis; it is misleading to think of these as separate entities.

The mortality rate with the various methods of treatment was as follows: conservative (347 cases), 37 per cent; surgical (369 cases), 2.1 per cent; and anticoagulant (32 cases), 29 per cent.

Bilateral division of the superficial femoral veins should be performed as soon as the diagnosis of phlebitis is made. If there are thigh signs (edema, tenderness and evidence of trauma) the common femoral vein should be divided. When clots are adherent or difficult to extract, further treatment (anticoagulants or ligation of the vena cava) is indicated.

Phlebitis should be actively treated before embolization occurs since 84 per cent of the initial emboli in this series were fatal.

The postphlebitic syndrome is associated with the severity of the phlebitis rather than the type of treatment.

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METHYPRYLON

A New Sedative and Hypnotic Drug

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THE purpose of this study was to evaluate the safety and efficacy of methyprylon (3,3-diethyl-2,4-dioxo-5-methylpiperidine),§ a central-nervous-system depressant, which in laboratory animals had shown a very desirable therapeutic ratio. The program, which was carried out on patients from the population of Long Island Hospital in Boston, consisted of three phases: a pilot experiment to determine whether methyprylon has somnifacient effects in man; a study of chronic toxicity to investigate the safety of the drug if it is given over a prolonged period; and a double blind study of the dose-response relation, including three dosage levels of methyprylon and placebo medication. This was followed by a limited-use test.

PILOT EXPERIMENT

Thirty-one hospitalized, chronically ill patients with very severe insomnia were chosen. They all were to be given (at 8:30 p.m.) 500 mg. of methyprylon for seven consecutive nights, 750 mg. for another week and placebo medication for three nights.

The three materials, which had been provided in the form of tablets simulating each other in size, color, shape and taste, were administered in a random sequence. Neither the observers nor the patients were aware, at any point during the experiment, of the identity of the medication, but we were. Rounds were made by trained personnel at thirty-minute intervals to determine the onset of sleep. From these recordings, average induction periods were calculated. Moreover, each morning the patients were interviewed to elicit their own appraisal of the quality of their sleep. This was recorded as poor, fair, good or excellent, depending solely on the patients' subjective evaluation. It took an average of almost two and a half hours for these patients to fall asleep after intake of the inert tablets (Table 1). Moreover, it appears that this induction period was reduced to an average of approximately forty minutes and twenty-six minutes, respectively, when these patients received 500-mg. and 750-mg. doses of methyprylon.

TABLE 1. *Average Time Required for 31 Patients to Fall Asleep after Placebo Medication and Methyprylon at Two Dosage Levels.*

TIME REQUIRED FOR PATIENT TO FALL ASLEEP ON PLACEBO MEDICATION	TIME REQUIRED FOR PATIENT TO FALL ASLEEP ON METHYPRYLON MEDICATION	
	500-MG. DOSE	750-MG. DOSE
min.	*min.*	*min.*
148.2	39.9	26.4

Table 2 presents the percentages of occasions on which the 31 patients were asleep at the various times of observation. The figures shown were calculated as follows: the total number of times that the patients were found to be asleep at a given hour of observation, on each night on which they had received a given medication, were multiplied by 100 and, for both methyprylon doses, divided by 217 (7 days of medication x 31 patients) and, for the placebo medication, by 93 (3 days of medication x 31 patients). It is seen that at these levels, methyprylon is a potent hypnotic as evidenced by the fact that the patients were asleep on almost all occasions an hour after the intake of 750 mg. and an hour and a half

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§Methyprylon is the generic name for 3,3-diethyl-2,4-dioxo-5-methylpiperidine. Originally designated Ro1-6463, this drug was supplied for this study as Noludar through the courtesy of Dr. Leo A. Pirk, of Hoffmann-La Roche, Incorporated, Nutley, New Jersey.

after the ingestion of 500 mg. of the drug. In contrast, with placebo medication, not all patients were asleep three hours after they had received the inert material.

Table 3 summarizes the results of the canvass of the patients' subjective appraisal of their sleep. The figures indicate percentages of ratings of which there were 217 after each of the two methyprylon dose levels and 93 after the placebo medication. The patients rated their quality of sleep as good or excellent after they had received 500 mg. of methyprylon and as excellent after the 750-mg. dose, both on over 96 per cent of the occasions. There were none, however, on any occasion, who rated their sleep as poor at either dosage level. On the other hand, after these patients had received placebo medication, they appraised their sleep as poor on over 80 per cent of the occasions, and there were none who considered it good or excellent.

Very few side effects were spontaneously reported. Four patients complained of headache on the mornings after intake of 750 mg. of methyprylon, but this did not persist.

Obviously, then, the drug under investigation had marked sedative and hypnotic qualities. Before a more detailed study of the usefulness of methyprylon was undertaken, its safety had to be investigated.

Chronic Toxicity

An important question was whether the prolonged administration of methyprylon had any untoward effect on the hematopoietic system.

Plan

Five hundred patients were to be included in the program. These were to have a week of observation without treatment (pretest period), to be followed by four weeks with daily administration of methyprylon (treatment period); then each patient was to have two weeks without medication (follow-up period), and this was to be followed by a week with daily administration of methyprylon (re-exposure period).

Table 2. *Occasions on Which 31 Patients Were Asleep at the Various Times of Observation after Placebo Medication and Methyprylon at Two Dosage Levels.*

Hour of Observation	Percentage of Patients Asleep on Placebo Medication	Percentage of Patients Asleep on Methyprylon Medication	
		500-mg. dose	750-mg. dose
p.m.			
8:30	—	—	—
9:00	—	34.10	64.98
9:30	—	85.71	98.16
10:00	—	98.62	99.54
10:30	9.68	99.08	100.00
11:00	53.77	99.54	100.00
11:30	92.48	100.00	100.00

For every patient the following laboratory work was planned: a complete hemogram (leukocyte count, erythrocyte count, hemoglobin determination, differential count and thrombocyte count) was to be performed initially, at the end of the treatment period and at the end of the follow-up period; a white-cell-count and hemoglobin determination were to be done at the end of the pretest period, at the end of the first, second and third weeks of the treatment period, at the end of the first follow-up week, on the second day of the re-exposure week and on the first day of the following week; in addition, urinalyses were to be done at strategic stages, and side effects on the gastrointestinal tract, central nervous system, cardiorespiratory system and skin were to be observed.

Table 3. *Subjective Appraisal of Quality of Sleep by 31 Patients.*

Rating	Percentage Regarding Placebo Medication	Percentage Regarding Methyprylon Medication	
		500-mg. dose	750-mg. dose
Poor	80.7	—	—
Fair	19.3	3.7	.9
Good	—	24.4	2.8
Excellent	—	71.9	96.3

As for dosage of methyprylon no definite plan was made except that the maximum tolerated dose would be given. We thought of administering, during both the treatment and re-exposure periods, a daily dose of 1 gm., or four or five times the dose reported by European workers[1] to induce sleep in patients with mild or medium insomnia, but, as pointed out below, we had to deviate from this dosage plan.

Execution and Results

Five hundred hospitalized, chronically ill patients — 254 males and 246 females — were studied whose ages ranged from thirty-three to ninety-six years, with an average of sixty-nine and seven-tenths years. The total series was divided into two groups of 250 patients each.

In the first group, patients were introduced at a rate of 10 per day, excluding Saturdays and Sundays, or at a rate of 50 per week. The study was so organized that after each subgroup of 50 had been introduced, no further patients were included for the following week so that each subgroup was started at biweekly intervals. The study of the second group of 250 patients was so arranged that each subgroup of 50 patients was introduced at weekly intervals.

A considerable number of side effects, such as excessive drowsiness, dizziness and even syncope, were encountered initially when the first group of patients received the massive dose of 1 gm., according to the original intention. Therefore, the daily dose had to be reduced. Subsequently, we attempted to increase the daily dose, and when side effects occurred again,

a lower dose was instituted, and so on. To compensate for any deficit in the total dose the period of medication was extended from four weeks, as originally planned, to six to fifteen weeks of daily administration.

However, the general lay-out of the experimental design was maintained. The actual duration of treatment in days and the actual dose range of methyprylon in milligrams, as they pertain to the five subgroups of patients during the treatment period for the first 250 patients, are given in Table 4.

TABLE 4. *Duration of Treatment and Dosage Range.*

PATIENT NO.	DURATION OF TREATMENT	DOSAGE RANGE
	days	*mg.*
1 - 50	93 - 107	45,500 - 53,750
51 - 100	81 - 95	40,625 - 49,250
101 - 150	67 - 77	32,375 - 38,875
151 - 200	53 - 66	25,375 - 33,375
201 - 250	40 - 49	19,875 - 26,000

In addition to the doses recorded, all 250 patients received a nightly dose of 500 mg. during the re-exposure week. Thus, the total dose of methyprylon ingested by this group of 250 patients ranged from 23.375 to 57.25 gm. per patient.

The hematologic work was carried out in accordance with the original plan and, in addition, several white-cell counts and hemoglobin determinations were done at strategic intervals during the treatment period because of its extension beyond the originally scheduled scope.

Urinalyses were carried out initially, at the end of the treatment period, at the end of the follow-up period, on the second day of the re-exposure week and terminally.

There were no untoward effects on the blood picture or on the urine in any of the patients studied in this group.

The following side effects were recorded on 103 occasions among the first 250 patients: drowsiness in 47, dizziness in 38, nausea in 2, vomiting in 4, and syncope (usually at a dose of 625 mg.) in 12 patients. These side effects occurred in a total of 49 patients; 201 patients had no reactions.

In view of the experience gained in the first 250 patients, the study of the second group of 250 patients was so organized that each patient received a nightly dose of 250 mg. of methyprylon for a week and this was increased to 500 mg. nightly at the beginning of the second treatment week and continued for five weeks. Thus, during the treatment period of six weeks, each patient of this group ingested 19.25 gm. of methyprylon. As in the first group, after a medication-free interval of two weeks, all patients were re-exposed to the drug at nightly doses of 500 mg. for a week. Consequently, each patient in the second group was given a total dose of 22.75 gm. The blood work was carried out in accordance with the original plan, and, in addition, white-cell counts and hemoglobin determinations were done at the end of the fourth and fifth treatment weeks because of the extension of the program beyond the originally scheduled scope.

Urinalyses were done initially, at the end of the treatment period, at the end of the follow-up period, on the second day of the re-exposure week and terminally.

As in the first group of 250 patients the blood picture and the urinary findings showed no significant deviations from those during the premedication period.

The following side effects were recorded on 44 occasions for the second group of 250 patients: drowsiness in 12, nausea in 8, vomiting in 9, headache in 10 and diarrhea in 5 patients. These side effects occurred in a total of 23 patients; 227 had encountered no reactions. If the side effects in the first and second groups are compared it is obvious that the smaller dosage in the second group was accompanied by fewer reactions.

With this evidence that the prolonged administration of massive doses of methyprylon and re-exposure to the drug at high dosage levels had no untoward effects on the hematopoietic system, a study of the dose-response relation was undertaken.

DOSE-RESPONSE RELATION

The purpose of this phase of the program was to determine whether doses of methyprylon smaller than 500 mg., which had been found very effective in the pilot experiment, would produce sleep and whether different levels of the drug would result in significantly different hypnotic effects. The doses of methyprylon chosen arbitrarily for that purpose were 150, 200 and 250 mg. Tablets containing these doses and placebo tablets, all simulating each other in size, color, shape and taste, were provided by the manufacturer under the code designations "W", "X", "Y" and "Z". We ourselves, as well as observers and patients, were unaware of the identity of these materials. In addition inert tablets of identical appearance were supplied, and it was made known to us, but not to the observers and patients, that these were placebo tablets.

Patients were to receive one tablet of each of the coded drugs for ten successive nights. Between these periods "known" placebo medication was to be introduced for three-day periods to prevent misinterpretation of observations as the result of an overlapping effect of the preceding drug.

One hundred and thirty patients with definite evidence of insomnia were selected for these trials. The sequence of drug administration was determined for each patient at random. The drugs were given at approximately 8:30 p.m. — the time the patients retired. All patients were observed subsequently at

half-hour intervals until midnight, to determine when they had fallen asleep. Any patient who was found asleep at a given round was further observed on the following rounds to establish whether sleep had been interrupted. All observations were recorded on cards, and, after the completion of the clinical study, the data elicited for the 110 patients who completed the program were transferred to master sheets for analysis.

For expression of results, the maximum hypnotic effect of a given drug, at a given time, was designated as 100 per cent effectiveness of that drug for that particular time. Obviously, this term implied that 110 patients who had received a given drug were found asleep, at a given time, on ten nights, or on 1100 occasions. Results with each of the four unknown materials were expressed for each of the intervals at which readings were taken as percentage of maximum hypnotic effect in accordance with this definition.

Although the decoding of the materials was done only after evaluation of the observations made, the drugs are identified below for greater ease of understanding.

The percentages of maximum hypnotic effects, at half-hour intervals, with each of the four materials used, are presented in the middle section of Table 5. In the right-hand section of this table the results obtained in the pilot experiment, in a different group of patients, with 500 and 750 mg. of methyprylon are added.

Figure 1 presents these same findings in graphic form.

The differences in the percentages listed for "Y", "X", "W" and "Z" in Table 5 and shown graphically in Figure 1 were found to be significant at the 1 per cent level. On the basis of these findings the view was expressed that "Y" was the placebo medication, "X" the 150-mg. dose, "W" the 200-mg. dose and "Z" the 250-mg. dose. At this point the materials were decoded, and the validity of our findings was confirmed.

It appears that, at all levels used, methyprylon produced sleep and that best results in the present trials were obtained with the 250-mg. dose. Findings with the 200-mg. dose were only slightly less favorable from a clinical point of view. The results at these two levels are shown in Table 6.

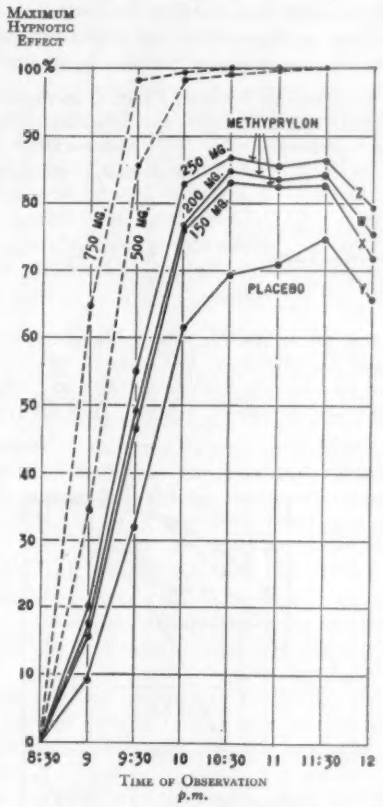

Figure 1. *Graphic Presentation of Findings, As Recorded in Table 5.*
The dotted lines indicate the results in a previous study with 500 and 750 mg. of methyprylon.

Table 5. *Maximum Hypnotic Effect Determined for 110 Patients at Various Levels of Methyprylon.*

Time of Observation	Maximum Effect with Placebo	Maximum Effect with 150 Mg. of Methyprylon	Maximum Effect with 200 Mg. of Methyprylon	Maximum Effect with 250 Mg. of Methyprylon	Maximum Effect with 500 Mg. of Methyprylon*	Maximum Effect with 750 Mg. of Methyprylon*
	(y)†	(x)†	(w)†	(z)†		
	%	%	%	%	%	%
9:00 p.m.	9.7	16.0	17.6	20.0	34.1	64.9
9:30 p.m.	32.1	46.8	49.1	55.1	85.7	98.2
10:00 p.m.	61.8	76.4	76.6	83.1	98.6	99.5
10:30 p.m.	69.4	83.1	85.1	87.1	99.1	100.0
11:00 p.m.	71.0	82.4	83.4	85.4	99.5	100.0
11:30 p.m.	74.7	82.8	84.4	86.4	100.0	100.0
12:00 midnight	65.7	71.3	75.2	79.3	(No observations)	

*Results taken from pilot experiment.
†Code designations under which materials supplied.

Throughout the study, observations were made for side effects. No reactions of any kind were spontaneously reported or elicited by the nurses.

Against the background of the results obtained in the study of dose-response relation a use test was carried out on a limited scale. This included 285 chronically ill patients — 190 females and 95 males — whose ages ranged from twenty-five to ninety-five years (average, fifty-seven years). They all required hypnotic medication and were given, at first, 200 mg. of methyprylon. This dose resulted in a comfortable night's rest in 243 cases but was inadequate in 42, in which 400 mg. was given subsequently with good results. Repeated doses of methyprylon were administered to the majority of the 285 patients. The total number of doses was 850. In general, sleep was induced within thirty minutes. The duration of effect could not be determined because of lack of technical personnel. However, all patients stated that they derived comfortable sleep from the medication. No side effects were encountered. It is particularly noteworthy that there was no "hangover."

TABLE 6. *Maximum Hypnotic Effects of Methyprylon.*

TIME OF OBSERVATION	MAXIMUM EFFECT	
	250-MG. DOSE	200-MG. DOSE
	%	%
At 1-hr. reading	55	49
At 1½-hr. reading	83	77
At 2-hr. reading	87	85

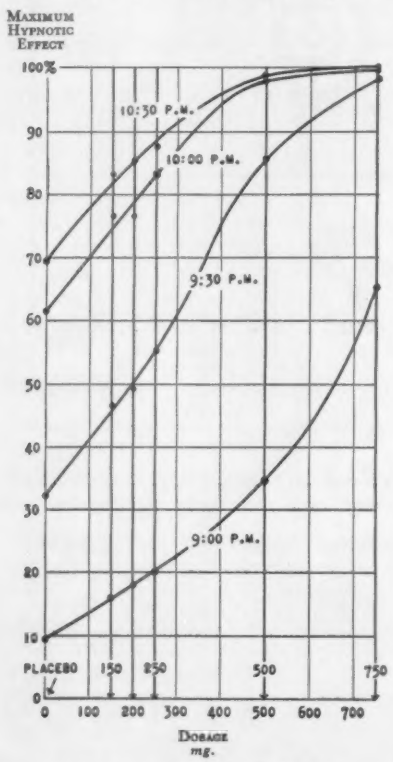

FIGURE 2. *Estimation of Effectiveness of Methyprylon for Dosage Levels besides Those Actually Used.*

Each curve presents the relation between dosage levels and percentages of maximum hypnotic effects half an hour, an hour, an hour and a half and two hours after drug intake.

DISCUSSION

No doubt the barbiturates are the most widely used sedative hypnotics. Since they have several objectionable features, however, a drug that does not belong to this class of compounds and is safe and effective is a definite desideratum.

As is evident from the findings in the trials of chronic toxicity, carried out in 500 subjects and discussed above, methyprylon is a safe drug from a hematologic point of view — that is, in all likelihood, it will not produce anemic, leukopenic or granulocytopenic reactions. Brandman et al.[2] carried out a similar project. These workers, too, gave excessively large doses of methyprylon over a prolonged period to 500 patients, who, after a rest period of two weeks, were re-exposed to the drug at a high level of dosage for a week. In these cases, as in ours, frequent hematologic investigations failed to reveal any toxic effects on the hematopoietic system. Loughlin and his associates[3] reported that the administration of methyprylon in therapeutic doses to 200 patients daily for eight weeks "caused no untoward hematic effects." Thus, laboratory data available on a total of 1200 patients, of whom 1000 received methyprylon in doses far in excess of therapeutic levels, showed no significant changes of the blood picture. Similarly, no aberrations in urinary findings were detected in any of these 1200 patients.

TABLE 7. *Estimated Responses to Various Dosage Levels of Methyprylon.*

TIME	MAXIMUM HYPNOTIC EFFECT ON 100 MG.	MAXIMUM HYPNOTIC EFFECT ON 300 MG.	MAXIMUM HYPNOTIC EFFECT ON 350 MG.	MAXIMUM HYPNOTIC EFFECT ON 400 MG.	MAXIMUM HYPNOTIC EFFECT ON 450 MG.
p.m.	%	%	%	%	%
9:00	13.5	22.5	25	28.0	31
9:30	41.0	61.0	67	73.5	80
10:00	70.0	87.0	91	94.5	97
10:30	78.5	91.0	94	96.0	98

No side effects were encountered in our patients who were given methyprylon in doses ranging from 100 to 500 mg. Brandman et al.,[2] who administered 250-mg. doses for night sedation to over 1000 patients, reported drowsiness and vertigo in only 1.3 per cent and no oversedation or vertigo in the 510 patients included in their daytime sedation study. Similarly, Loughlin and his co-workers[3] stated that methyprylon "produced a minimum of side reactions

which, when they occurred, were mild and disappeared mostly after one week of medication."

There can be no doubt from the first and third phases of our studies and those of the two other groups of workers[2,3] that methyprylon is an effective sedative and hypnotic. From the double blind study of dose-response relation described above, it appears that in our particular sample 250 mg. of methyprylon produced sleep after an hour and a half in 83 per cent of the 1100 occasions on which observations were made at this interval. Findings with the 200-mg. dose were only slightly less favorable.

By plotting of percentages of maximum hypnotic effect in the present study and in the pilot experiment against the doses of methyprylon used, curves could be drawn representing the effects of different dosage levels at different times (Fig. 2). From this graph it was possible to interpolate effects to be expected from 100, 300, 350, 400 and 450 mg. of methyprylon.

As appears from Table 7, which shows the estimated responses from dosage levels other than those employed in the double blind study, 300 and 400 mg. of methyprylon may be expected to produce sleep after an hour and a half, respectively, in 87 per cent and 94 per cent of the 1100 observations. From this it seems that 300 or 400 mg. of methyprylon would induce sleep in a higher percentage of cases than 200 or 250 mg. The use test showed that, in general, 200 mg. is an adequate dose for night sedation, but that some patients require 400 mg.

Since the requirements of hypnotic drugs may vary greatly from patient to patient and since an attempt should always be made to reach a therapeutic objective with the minimal effective dose, it is suggested that in cases of mild and medium insomnia in adults, 200 mg. be given initially. If this does not have the desired effect, 300 and, if necessary, 400 mg. may be administered.

Summary and Conclusions

Thirty-one patients with severe insomnia were given two dosage levels of methyprylon (Noludar) and placebo medication. The average induction period of almost two and a half hours with the inert material was reduced to approximately forty minutes and twenty-six minutes respectively when 500 and 750 mg. of the drug were administered.

The hematic effects of prolonged daily administration of methyprylon in excess of therapeutic doses were studied in 500 patients who, after a rest period of two weeks, were re-exposed to large doses of the drug for a week. Frequent hematologic investigations failed to show any aberrations of the blood picture.

A double blind study with three dosage levels of methyprylon — 150, 200 and 250 mg. — and with placebo medication was carried out in 110 patients who required night sedation. They all received the four materials for ten nights each. Recording of the responses at half-hour intervals and evaluation of the findings made it possible to identify correctly the drugs that had been supplied under code designations. At all dosage levels methyprylon produced sleep, but the 250-mg. dose was more effective than the two lower doses used. Analysis of results showed that the differences of findings are statistically significant, and that there is a good dose-response relation.

A use test was carried out in 285 chronically ill patients who were given a total of 850 doses of methyprylon; 200 mg. in 243 of these subjects and 400 mg. in 42 produced satisfactory results.

It is concluded that the drug is a safe and effective sedative-hypnotic.

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THE SYNDROME OF THE HYPERSENSITIVE XIPHOID*

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MANY patients complain of pains in the chest, upper abdomen and shoulders that are not characteristic of any familiar disease. In the past seven years 24 patients have been observed in whom gentle pressure on an extraordinarily hypersensitive portion of the xiphoid reproduced much or all of their pain. Some of them had coronary-artery, arthritic, gastric, duodenal, gall-bladder or esophageal disease; others, however, seemed healthy except for their discomfort and tenderness. The xiphoid is not often examined routinely even in careful physical examinations. It is with the hope of encouraging further study of the hypersensitive xiphoid that this report is presented.

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Review of the Literature

An exhaustive summary of the literature is to be found in the small monograph by Burman and Sinberg.[1] Observations on disorders of the xiphoid were recorded as early as 1712.[2] The first curative xiphoidectomy was done in 1852,[3] on a xiphoid bent posteriorly; pressure caused pain and vomiting, which peared on sudden rising from a stooped position. Most of his patients were treated successfully by infiltration with procaine. Various authors[7-9] have described surgical approaches to the xiphoid, the technics of examination[10,11] and the anatomic variations.[12-14] da Silva-Mello[15] wrote that pain in the xiphoid was a valuable — sometimes the only — sign of abdominal disease, especially peptic ulcer.

Table 1. *Clinical Data in 24 Cases of Tender Xiphoid.*

Patients	Age at Onset yr.	Associated Disease	Duration	No. of Recurrences	Site of Pain	
					primary	radiation
M.T.	43	Cholelithiasis, with cholecystectomy; myocardial infarct; anginal syndrome.	18 mo.	1	Midportion of chest	Shoulders & back
B.A.	55	Coronary-artery disease; peptic ulcer.	1 yr.	1	Chest & epigastrium	Left hand
G.S.	30	Hypertension	6 mo.	0	Lower midportion of chest; upper epigastrium.	None
H.J.	48	Psychoneurosis	2 yr.	0	Midportion of chest	Throat
N.F.	51	Obesity; osteoarthritis.	3 mo.	0	Over xiphoid	Left shoulder
A.J.	32	None	1 mo.	0	Left pectoral area	Left shoulder
H.E.	44	Cholelithiasis, with cholecystectomy	About 2 yr.	1	Xiphoid — then sternum	Throat; left shoulder.
A.M.	74	2 myocardial infarcts; advanced arteriosclerosis, generalized; diabetes; pneumonia.	3 wk.	1	Precordium	Left shoulder
A.W.	51	Obesity; epigastric hernia (?).	Each episode 2-6 wk.	5	Fullness in midportion of chest	Back & shoulders
M.G.	49	Cervical disk (1 yr. later)	6 mo.	0	Xiphoid area	None
J.G.	53	Cholelithiasis, with operation	3 mo.	1	Epigastric area	Back
S.H.	46	None	3 mo.	0	Lower sternum	None
E.L.	40	Gastritis; duodenitis; ulcer(?); prolapse of gastric mucosa.	6 yr.	1	Chest; upper epigastrium.	None
M.L.	40	Hiatus hernia; cervical disk.	5 mo.	0	Chest (sternal area)	Shoulders
T.B.	50	Obesity; anginal syndrome; myocardial infarct.	3 yr.	0	Sternal area	Left arm & hand
H.K.	53	Myocardial infarct; psychoneurosis.	5 yr.?		Center of chest	None
N.K.	53	Arthritis of spine	±1 yr.	0	Midportion of chest	None
V.H.	53	Arthritis of spine	4 mo.	0	Sternum; right lower ribs.	None
N.D.	52	Osteoarthritis	8 mo.	0	Sternum	Left axilla & arm
P.B.	59	Obesity; hypertension.	15 mo.	2	Midportion of chest	Back; epigastrium; shoulders.
M.B.	74	Cholelithiasis; polyp of duodenum; esophageal diverticulum.	4 yr.	3	Epigastrium	Back
B.S.	41	Hypothyroidism	3 yr.	1	Substernal area	None
C.R.	48	Hyperacidity (no ulcer on x-ray study); osteoarthritis; negative x-ray study of xiphoid.	±1 yr.	1	Lower sternal area	Left breast
C.L.	50+	Hypertensive heart disease; arthritis of hand & spine; right-bundle-branch block.	2 yr.	1	Left mammary region	Left shoulder & arm to fingers; left intrascapular area.

could be avoided if the patient remained supine after eating. Zadek,[4] in 1941, and Hanlon and Miller,[5] in 1954, each reported 1 case with severe symptoms, including pain in the upper abdomen, nausea and vomiting, relieved by the removal of a "tack-hammer" xiphoid displaced posteriorly.

Junghanns[6] likened xiphoidalgia to coccygeal pain. He noted the appearance of xiphoid pain in men who had resumed heavy work after long inactivity. He considered this a form of strain since the pain ap-

Fenz,[11] on examining 4000 hospitalized patients, found pain and tenderness of the xiphoid in 84. Forty-five of these had hypertensive heart disease, including 20 with angina pectoris. Fenz noted that several of the remaining 39 had gastrointestinal disease (ulcer in 8 and gastritis in 6) and suggested that the xiphoidalgia might be secondary to the alimentary-tract lesion. Xiphoidalgia may also result from a number of local injuries.

In certain cases the associated pathologic process

is obscure. Ruediger[16] reported 3 cases in which a painful xiphoid was removed and showed "perichondritis." Fenz[11] described 2 cases of "rheumatic apophysitis" of the xiphoid.

Secondary xiphoidalgia, in association with gallbladder disease, peptic ulcer, hiatus hernia, prolapsed gastric mucosa, gastritis, angina pectoris or esophageal disease, need not be accompanied by local pathologic changes in the xiphoid. However, Narat[17,18] removed the xiphoids in 5 cases of xiphoidalgia and found "subacute periostitis" in all. Four of these patients had gastric ulcers, suggesting that true "secondary xiphoiditis" may exist. Adequate pathological studies are, unfortunately, lacking. It seems preferable to postulate the occurrence of xiphoidalgia in conjunction with peptic ulcer and other diseases as an example of referred pain and hyperalgesia, even though it is impossible at present to delineate the precise nervous pathways.

TABLE 1 *(Concluded).*

PATIENTS	SEVERITY	ASSOCIATED SYMPTOM	EFFECT OF ETHYL CHLORIDE	EFFECT OF PROCAINE	REMARKS
M.T.	+++	Nausea	Partial relief	Not tried	Pain before & persisted after operation
B.A.	+++	Angina	Partial relief	Not tried	
G.S.	++	None	Not tried	Not tried	Tomogram normal
H.J.	++	Anxiety	Not tried	90%	
N.F.	++	Nausea	Not tried	Not tried	
A.J.	++	Faintness	Not tried	Not tried	
H.E.	+++	None	Not tried	Not tried	
A.M.	++	None	Not tried	Transient relief	Xiphoid pain & tenderness preceded each infarct
A.W.	++	None	Partial relief	Partial relief	
M.G.	++	None	Not tried	Not tried	
J.G.	++	None	Not tried	Not tried	
S.H.	++	None	Not tried	Not tried	
E.L.	++ to +++	Heartburn	Slight relief	Not tried	
M.L.	+++	Slight nausea; faintness.	Not tried	Not tried	
T.B.	++	Cold left hand	None	Marked relief	Patient of Dr. Harold Leder
H.K.	++	Belching	Marked relief	Not tried	
N.K.	++	None	Not tried	Not tried	
V.H.	++	None	Not tried	Not tried	
N.D.	++	Nausea	Not tried	Not tried	
P.B.	+++	Nausea	Transient relief	?	
M.B.	+++ to ++++	Anxiety	Not tried	Not tried	
B.S.	+++	Faintness	Not tried	Not tried	
C.R.	++	Pain on belching	Not tried	Not tried	
C.L.	++	Choking & pain in left upper quadrant of abdomen after meals	Not tried	Marked relief	Patient of Dr. Elliot Hochstein

OBSERVATIONS

Two hundred consecutive unselected ward patients were examined. Tender xiphoids were found in 6, 4 of whom complained of chest symptoms strongly suggesting the xiphoid syndrome. In the 2 patients without chest pain the diagnoses were cholecystitis and prostatitis combined with phlebitis. Of the 4 with the xiphoid syndrome 1 had been admitted for study of the peculiar chest symptoms; findings were normal except for xiphoid tenderness. The other 3 had arteriosclerotic, rheumatic and hypertensive heart disease respectively.

In brief, of the 6 cases of abnormally tender xiphoid

among 200 patients, heart disease was known to be present in 3. Of the total group of 200 patients 51 had heart disease — a prevalence of 6 per cent of tender xiphoids in ward cardiac patients. It should be noted that 7 of the 200 patients had gall-bladder disease; 1 of these had a slightly tender, and 1 a very tender xiphoid. In general, our observations are in agreement with those of Fenz.[11]

The youngest patient in our group was a girl of twenty-three, and the oldest a man of seventy-four. Most of the patients were forty to sixty years of age, as were most of the ward population. Table 1 summarizes the data on the 24 patients with extremely tender xiphoids observed clinically in the past seven years.

Xiphoidalgia without Other Known Diseases

Most of the 10 patients in the group knew of some activity or change of position that precipitated the discomfort. In all cases the symptoms could be reproduced by gentle xiphoid pressure.

Case 1. H.J., a 48-year-old insurance executive, was first seen in January, 1954. Since 1952 he had had an intermittent sensation of pressure and tightness in the chest and upper abdomen, occasionally radiating to the throat. These symptoms commonly occurred while he was hurrying to catch his evening train but never compelled him to slow down. He had been referred by his psychiatrist, Dr. B. C. Glueck, Jr., who considered these chest symptoms, which aroused much anxiety in the patient, not related to the neurosis. There were no relevant physical findings except extreme tenderness of the lower left margin of the xiphoid, where pressure duplicated most of the long-standing symptoms. Studies at the New York Hospital, including an electrocardiogram, an exercise-tolerance test and x-ray films of the gall bladder, gastrointestinal tract and chest, revealed normal findings.

On the last day in the hospital attempts were made to inject the tender area with procaine. The first injection was made with the needle directed at a point approximately 0.5 to 1 cm. above the lowest margin of the xiphoid. The patient experienced partial relief of the tenderness. Pressure at the lowermost corner still produced the sickening sensation in the center of the chest. About 20 minutes later, another infiltration was done, this time at the level of the lower margin. Within 2 minutes pressure no longer elicited pain, nor did walking rapidly down a series of long corridors carrying a heavy bag in each hand. During the next 6 months there were mild recurrences on 3 occasions, always relieved by infiltration with procaine. Examination showed no definite tenderness of the xiphoid. Recently, he noticed some discomfort in the center of the chest while bending over; there have been no symptoms on exertion.

This case illustrates the resemblance to angina including the precipitation of the pain by rapid walking, the anxiety aroused and the central location. The bizarre characteristics of the sensations and the high degree of relief with procaine infiltration are noteworthy. It is unlikely that the relief was due to suggestion because, on two occasions, injection 1 cm. or less away caused only minimal improvement.

Case 2. A.J., a 32-year-old physician, was first seen on March 18, 1953, complaining of dull but very annoying pain in the left shoulder of 12 days' duration that also involved the left pectoral area and left upper arm. The pain was frightening because it usually appeared when he was walking up an incline, although it occasionally occurred during inactivity. Gentle pressure on the xiphoid produced a great increase in the shoulder pain, which persisted for 36 hours, in combination with a new and persistent pain in the xiphoid area. Xiphoid pressure by the examiner or by the patient made the patient blanch and feel faint. He then became symptom free for about 1 week but awoke from sleep one morning with the same pain and noted that he had been lying on his arm in such a manner that there was pressure on the xiphoid. The pain persisted for several hours. Serial electrocardiograms were normal. The pain disappeared spontaneously after a few weeks.

This case illustrates again the curious resemblance of this discomfort to angina pectoris in that walking up an incline produced the symptoms although they also occurred while the patient was resting quietly.

Xiphoidalgia and Concomitant Coronary-Artery Disease

Case 3. B.A., a 55-year-old physician, was first seen in 1952 complaining of episodic pain in the anterior aspect of the chest since 1947 that varied in precise location and in precipitating circumstances. The pain was usually in the substernal area and often radiated to the neck and left arm. When associated with activity it was sufficiently severe to induce him to stop. With the onset of pain in 1947 coronary-artery disease was diagnosed, and after 2 months of bed rest, he had experienced some relief. In 1948 a peptic ulcer was found; on a strict ulcer regimen the substernal pain disappeared. Early in 1952 he began to have increasingly frequent pain in the lower sternal area, with simultaneous pain in the fingers of the left hand, precipitated by walking and lasting 10 minutes to 2 hours. The pain did not compel him to stop activity and occasionally occurred during rest. During physical examination, pressure on the xiphoid reproduced the pain and also caused faintness, blanching and sweating. When next seen he reported that the pain induced by the gentle xiphoid examination had lasted for 10 hours and was located in the xiphoid area and referred down the left arm. An exercise-tolerance test pointed to coronary-artery disease.

Because the patient was sensitive to procaine, ethyl chloride was sprayed over the xiphoid area, with considerable relief. He obtained an ethyl chloride bottle of his own and sprayed himself so frequently that the skin over the xiphoid became blistered. However, he became able to walk without provoking chest pain. At present he is free of these symptoms, though on a regimen of reduced activity.

Three other patients had xiphoidalgia apparently in association with coronary-artery disease. In 1, xiphoidalgia appeared to have developed as a prodromal manifestation of myocardial infarction on two occasions.

Xiphoidalgia with Gall-Bladder Disease

Case 4. H.E., a 44-year-old man, complained of a dull, nagging pain in the upper abdomen. In early 1949 examination revealed marked tenderness of the xiphoid. X-ray study showed gallstones. In July of that year acute cholecystitis necessitated cholecystectomy; in October the xiphoid was not tender. The patient was seen again in November, 1952, because for 4 months he had been having episodic discomfort in the chest and a sense of constriction in the throat. Often the pain seemed to radiate from the midportion of the chest to the left shoulder and was accompanied by a tingling of the left arm. The discomfort lasted from minutes to hours and was not related to activity. All symptoms, including the sense of throat constriction and left-arm discomfort, were reproduced by pressure on the xiphoid. An electrocardiogram was normal. The xiphoid remained tender for several months, and then the patient became asymptomatic spontaneously.

It is of interest that this patient's xiphoidalgia recurred after removal of what was assumed to be the primary disease.

CASE 5. M.T., a 43-year-old housewife, was seen in 1951 because of indigestion, nausea and vomiting. She had, in addition, a mild anginal syndrome that followed an acute myocardial infarction, probably the aftermath of surgical shock during a previous nephrectomy. X-ray study of the gallbladder region showed cholelithiasis. A few months later xiphoid tenderness appeared; the patient was then complaining of bouts of severe pain in both shoulders in addition to the abdominal pain. Cholecystectomy relieved the symptoms. The xiphoid remained tender to pressure for 8 months although during that time there was no spontaneous pain. After ethyl chloride sprays the tenderness disappeared.

OTHER CONDITIONS ASSOCIATED WITH XIPHOIDALGIA

CASE 6. M.L., a 40-year-old physician, began, in 1947, to experience pain over the lower portion of the sternum that often radiated up the center of the chest and occasionally to both shoulders and upper arms. It was of variable severity but, when intense, developed a sickening, nauseating quality. The pain most commonly occurred during exertion, but also at rest or when he was turning in bed. Each episode lasted between 15 and 20 minutes, and was of fairly rapid onset and slow disappearance. Occasionally, a dull but disturbing ache persisted for much of the day. Accidentally, he discovered that all his symptoms, in severe form, could be promptly induced by gentle pressure at a point on the right border of the xiphoid. He became apprehensive of even brief palpation of the xiphoid because gentle touch often produced the nauseating pain, which might persist for 15 to 30 minutes. Some months later, when tenderness was largely gone, he found a small nodule, 0.5 cm. in diameter, lying against the xiphoid at the point that was previously the site of great tenderness. The nodule was bony hard and movable, and felt somewhat like a sesamoid. In 1947 x-ray study of the chest, sternum, gastrointestinal tract (hiatus hernia was looked for and not found) and gall bladder was negative, and electrocardiograms were normal. In 1953 a hiatus hernia was first demonstrated. In addition, in 1953, this patient experienced pain in the left-shoulder area associated with numbness and tingling of the last 2 fingers. This proved to be due to a cervical disk.

This is another case that illustrates a superficial resemblance between the xiphoid syndrome and the discomfort of angina pectoris. Appearance of the nodule suggests the possibility that a localized osteochondritis was present. Burman and Sinberg[1] have described such findings.

DISCUSSION

Anatomic Considerations

The xiphoid varies considerably in size, shape and precise position. When situated anteriorly, it is readily palpated and often easily seen in thin people. When placed posteriorly, it may be difficult to feel, particularly if the costal angle is narrow. We have encountered a patient with a xiphoid over 6 cm. long and others with one of 2 cm. It may be forked or may show fenestration. It may be fairly pliable or rigid.

The anterior surface of the xiphoid serves as attachment for a small portion of the rectus abdominis muscle and for the costoxiphoid ligament. Posteriorly, fibers of the diaphragm and transversus thoracis are attached. The aponeuroses of the abdominal muscles attach along the lateral borders of the xiphoid. The precise innervation of the xiphoid has never been elucidated. The best known source of sensory fibers to the xiphoid consists of the spinal (fourth to eighth thoracic) nerves via the intercostal nerves. As the terminal filaments of these nerves approach the midline anteriorly they send fibers upward over the sternal area. These nerves also supply some areas of skin, to which pain and hyperalgesia may be referred from the stomach and gall bladder, in the mechanism of segmental spread of pain impulses described by Lewis.[19] Overlapping of xiphoid and cardiac afferent innervation occurs, since pain from the heart is transmitted over the dorsal rami of the first to sixth thoracic nerves[20] and from the xiphoid over the fourth to eighth thoracic nerves.

In addition afferent fibers reach the phrenic nerves from the xiphoid. The terminal fibers of the phrenic nerves, having pierced the diaphragm, ramify over the parietal peritoneum on the abdominal surface of the diaphragm and also send branches to the liver capsule. Phrenic innervation probably explains the referral of xiphoid pain to one or both shoulders, observed in certain cases. It appears that there is ample connection through the spinal and phrenic nerves to explain the varied and widespread sensory phenomena observed.

Symptoms and Signs

The *sine qua non* of the syndrome is the reproduction of the pain of which the patient has complained when the tender portion of the xiphoid is subjected to very moderate fingertip pressure. Most people complain of pain if the xiphoid is pressed forcefully; it is normally somewhat more tender than most other bones.

It has been useful to employ each patient as his own control. Before the xiphoid is touched the adjacent ribs, costal cartilages and sternum are subjected to forceful fingertip pressure, and the patient's responses are closely observed. The xiphoid is then gently palpated over its entire surface and along its borders, with much less pressure than that required to produce even mild discomfort over adjoining bones. In some patients the borders of the xiphoid are easily outlined. In others the margins of the bone may be difficult or impossible to palpate, and precise localization of the tenderness may not be possible. If the syndrome is present, an area of marked tenderness is found over some portion of the xiphoid, most commonly along a border. Usually, the patient, on inquiry, states that the pressure has produced not only local discomfort but also the pain in the chest, shoulder or throat, which he experiences spontaneously. In some cases the same gentle pressure must be maintained for a minute or two before the local discomfort increases and spreads. After palpation the pain may persist for minutes or hours. Indeed, some patients with the syndrome refuse further examination

of the area and palpate it themselves only with great care and obvious apprehension.

Occasional patients show moderate hyperesthesia of the xiphoid but have no history of spontaneous episodes of pain. The significance of this finding is obscure. One pitfall should be mentioned: some patients who are apprehensive may overreact to the curiously disconcerting sensation that may follow pressure on the xiphoid.

The pain of the xiphoid syndrome varies greatly in location, quality, severity, duration and precipitating agents — not only in different patients but also in the same patient at different times.

The pain is most commonly experienced deep in the chest somewhere behind the sternum and may radiate into the epigastrium, through to the back, to both shoulders, to the arms or over the precordium. Two patients had a feeling of constriction in the throat.

The pain is most commonly described as a deep, slightly nauseating ache, somewhat like that experienced after a blow in the celiac plexus. It is sometimes described as dull, rarely as burning and never, in our experience, as stabbing. It may be slight or great and is seldom agonizing. When it occurs at night it is often severe enough to interfere with sleep — sometimes because of the intensity of pain per se and sometimes because the deep visceral quality arouses much apprehension. When the pain appears during exertion, the patient may or may not stop his activity at once, in contrast to angina pectoris, which usually compels stopping.

The onset and disappearance of the pain are not instantaneous. The duration varies from minutes to many hours, with recurrences at intervals of minutes, hours or days. Usually, the pain recurs many times daily. The syndrome, if untreated, may last for weeks, more commonly for months and rarely for years, and has usually disappeared spontaneously. In occasional cases it has recurred months or years later.

The precipitating causes are often obscure and vary from patient to patient. Bending, stooping, lifting, turning over in bed, eating a large meal and walking, especially up an incline, are common causes of renewed pain.

Diagnosis

The diagnosis is easily made if the condition is suspected. Since the condition is not infrequent, it is suggested that palpation of the xiphoid area be done in most general physical examinations and certainly in all patients complaining of pain in the chest or upper abdomen, whether or not other disease is present. It is important that the observer routinely practice palpation of the xiphoid long enough to become familiar with the range of normal tenderness. Most xiphoids are more tender than other bones, but when this syndrome is present, remarkably little pressure is required to cause considerable pain and duplication of symptoms.

In view of the relatively frequent association of this syndrome with coronary-artery disease, gall-bladder disease, peptic ulcer, esophageal lesions and hiatus hernia the concomitant presence of these conditions should be considered.

Treatment

Procaine infiltration. Adequate procaine infiltration of the xiphoid area is the most effective means of producing lasting relief of pain. Sometimes, symptoms recur in milder form after some days, necessitating a second infiltration. Occasionally, it is necessary to block the region a third time before more lasting relief is obtained.

The mechanism by which procaine infiltration provides relief is a matter of speculation. The interruption of pain impulses in a self-perpetuating or reverberatory circuit is one explanation, as suggested by Travell.[20] Our observations offer no direct evidence on these points. No attempt has been made to control the psychologic effect of injections by the use of saline solution, but in 1 case, on two separate occasions, the patient received injections about 1 cm. from the critical area, with little relief, only to lose the pain completely when the injection was made in the most tender area.

Ethyl chloride spray. This may relieve symptoms during an attack; the prompt occurrence of relief may aid in the diagnosis. Ethyl chloride is not often effective in abolishing attacks permanently, but in occasional cases, prolonged relief ensues.

Treatment of the underlying disease. When xiphoidalgia occurs in association with other diseases, treatment directed toward symptomatic control of the major disease may be followed by disappearance of the xiphoidalgia. In cases in which the pain persists after operation procaine infiltration may be employed.

Reassurance. The pain arising from the xiphoid area characteristically produces anxiety. Usually, the patient believes that he has heart disease, and requires reassurance. Even when procaine infiltration fails, as it may, spontaneous disappearance of the pain within some weeks or months is to be expected.

Surgical excision. As stated above, xiphoidectomy has been performed in the past for relief of xiphoidalgia. Of the cases of xiphoidalgia that we have seen none have required excision. Operation seems indicated only in patients who have severe, prolonged pain that is unresponsive to other therapy.

It is hoped that those who have an opportunity to excise the xiphoid will report the details of the pathology, particularly the condition of nerve fibers, nerve endings and arteries.

Summary and Conclusions

The xiphoid syndrome has one common denominator — pressure on the very hypersensitive portion

of the xiphoid reproduces the varied chest, shoulder, arm, back or epigastric discomfort of which the patient complains.

The natural history, including frequency, anatomy, pathology, symptoms and signs, is described. Apparently, the syndrome can be found in roughly 2 per cent of the population of a general-hospital ward. It is seen without other known disease but somewhat more commonly in association with diseases of the heart, gall bladder, stomach and esophagus, and with osteoarthritis.

A series of 24 cases is reported.

Methods of treatment, including procaine infiltration, ethyl chloride spray, reassurance and excision, are described.

It is urged that this syndrome be searched for. It is believed to be far more common than is generally appreciated.

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PENTOLINIUM AND HEXAMETHONIUM COMBINED WITH RAUWOLFIA IN THE TREATMENT OF HYPERTENSION*

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IN the treatment of moderate to severe hypertension the experience of most investigators suggests that a centrally acting agent such as *Rauwolfia serpentina* combined with a ganglionic-blocking drug offers the most potent antihypertensive combination. Rauwolfia in combination with hexamethonium has been used effectively in the outpatient management of hypertension,[1] with satisfactory orthostatic reduction in blood pressure but with significant untoward effects attributable to the use of the hexamethonium. Since its introduction[2,3] to American clinics pentolinium has been reported to offer more prolonged ganglionic blockade, with less severe untoward effects, than hexamethonium.

This report is an evaluation of pentolinium used in combination with Rauwolfia in the management of a group of hypertensive patients (Group 2), and a comparison of pentolinium and hexamethonium when each was used in combination with Rauwolfia (Group 1) for the treatment of another group of patients with clinical hypertension. All patients were treated on an outpatient basis.

Method of Study

Seventy-five patients (Group 1) who had previously received Rauwolfia and hexamethonium for twelve to eighteen months were changed as an otherwise unselected group from Rauwolfia combined with hexamethonium to Rauwolfia and pentolinium.‖ At the initiation of the present study this constituted all patients who were receiving Rauwolfia and hexamethonium, whether responsive to treatment or not, who were being followed by us. Each patient in this part of the study served as his own control for a comparison of pentolinium with hexamethonium. Thirty-two of these patients were from the City-County Charity Hospital, and 36 were from the Veterans Administration Hospital; 7 were private patients incorporated with the Veterans Administration Hospital patients throughout this report. The patients in Group 2 consisted of 34 patients who received Rauwolfia in combination with pentolinium from the outset of treatment.

Each patient received a complete medical work-up

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‖Kindly supplied as Ansolysen by Wyeth Laboratories, Philadelphia.

before being referred to the hypertensive clinic for treatment. Routine laboratory studies included a complete blood count and urinalysis, a chest teleoroentgenogram, a determination of blood urea nitrogen and an electrocardiogram. All patients were placed on placebo therapy and were followed at weekly intervals for at least four weeks before definitive drug therapy was begun. Blood pressures were recorded in the standing and supine positions by a physician at each clinic visit, and a careful inventory of potential side effects was made. After the initiation of definitive drug therapy, follow-up visits were made at intervals of one to four weeks, being more frequent during the time when the dosage of the ganglionic agent was being adjusted to produce the optimal result. Both hexamethonium and pentolinium were administered by a titration method — that is, therapy was begun with small doses of the ganglionic-blocking agent and then increased until an optimal blood-pressure reduction was obtained or side effects prohibited further increase in dosage. By contrast, Rauwolfia compound was given as a fixed dose of 2 mg. of reserpine, 8 mg. of alseroxylon or 400 or 500 mg. of whole root (Rauwolfia) per twenty-four hours. The dose was usually divided and given with meals and at bedtime. Key laboratory studies (determination of blood urea nitrogen, electrocardiograms, urinalysis, and x-ray examination of the chest) were performed at intervals during treatment.

Patients in Group 1 who received Rauwolfia and hexamethonium before Rauwolfia and pentolinium received the latter combination for periods of three to eight months. All blood pressures recorded during this period were averaged. The results of treatment during this period were compared and contrasted with those similarly obtained during the period of three to six months of Rauwolfia combined with hexamethonium, immediately preceding change of their therapeutic program to Rauwolfia and pentolinium.

All patients in Group 2 received Rauwolfia with pentolinium from the start of combination therapy. Twenty-seven of these patients had severe hypertension requiring combination therapy from the start, and 7 had received Rauwolfia alone without an adequate blood-pressure response. These are included in the same group without distinction.

In both Group 1 and Group 2 the blood-pressure response is based on determination in the upright position. This is necessary in regulation of dosage because ganglionic blockade results in an orthostatic blood-pressure reduction predominantly, the reduction in supine levels being more delayed in onset and less prominent in magnitude. A "response" to therapy was defined as a reduction of 20 mm. of mercury or more in the mean pressure in the upright position; a patient was said to be normotensive if the average reading was 150 systolic, 100 diastolic, or less. If either systolic or diastolic average was greater than this, the patient was not considered to be normotensive.

TABLE 1. *Summary of Clinical Status of Patients before Treatment.*

GROUP	NO. OF PATIENTS TREATED	AVERAGE AGE	MALE PATIENTS	FEMALE PATIENTS	PATIENTS WITH RENAL DISEASE‡	PATIENTS WITH CARDIAC FAILURE‡	PATIENTS WITH ABNORMAL ELECTROCARDIOGRAM‡	PATIENTS WITH PREVIOUS MYOCARDIAL INFARCTION‡	PATIENTS WITH PREVIOUS CEREBROVASCULAR ACCIDENT‡	PATIENTS WITH NO FUNDUSCOPIC CHANGES	PATIENTS WITH GRADE 1 & 2 FUNDUSCOPIC CHANGE§	PATIENTS WITH GRADE 3 & 4 FUNDUSCOPIC CHANGE§
		yr.										
Group 1*:												
Responsive	59	53	30	29	26	41	42	7	6	2	43	14
Nonresponsive	16	51	9	7	6	9	9	0	0	3	9	4
Totals	75		39	36	32	50	51	7	6	5	52	18
Group 2†:												
Responsive	32	50	23	9	13	10	23	5	2	6	13	13
Nonresponsive	2	50	0	2	0	1	1	0	0	1	1	0
Totals	34		23	11	13	11	24	5	2	7	14	13

*Patients who first received Rauwolfia & hexamethonium & then switched to Rauwolfia & pentolinium.
†Patients who received Rauwolfia & pentolinium as initial therapy.
‡Number in respective groups with this complication.
§Graded 1 to 4, according to Keith–Wagener classification.

RESULTS

Group 1

This group consisted of 75 patients who had previously received Rauwolfia combined with hexamethonium for twelve to eighteen months. Blood-pressure response during the last three to six months of this therapy is compared with the results after three to eight months of Rauwolfia in combination with pentolinium. The clinical status of this group is listed in Table 1.

Fifty-nine of these patients, or 79 per cent, had a reduction of at least 20 mm. of mercury and were

considered responsive to pentolinium-Rauwolfia treatment (Table 2). Fifty-seven patients, or 76 per cent, were previously responsive to Rauwolfia combined with hexamethonium. Twenty-five patients, or 33 per cent, were normotensive on pentolinium-Rauwolfia therapy. Twelve who had not previously been responsive to Rauwolfia combined with hexamethonium were responsive to Rauwolfia and pentolinium. Ten who were responsive to Rauwolfia combined with hexamethonium did not respond to Rauwolfia and pentolinium.

Side effects, both beneficial and untoward, are analyzed in Table 3, with a comparison on the same patients of effects present during pentolinium therapy as compared with hexamethonium. Impotence, although present under both regimens in many cases, is not included because of difficulty in accurate evaluation.

TABLE 2. *Comparison of the Blood-Pressure Response to Rauwolfia Combined with Pentolinium and Rauwolfia Combined with Hexamethonium.*

SOURCE OF DATA	RESPONSE TO RAUWOLFIA & PENTOLINIUM				RESPONSE TO RAUWOLFIA & HEXAMETHONIUM			
	TOTAL NO. TREATED	RESPONSIVE PATIENTS†	NORMOTENSIVE PATIENTS	NONRESPONSIVE PATIENTS	TOTAL NO. TREATED	RESPONSIVE PATIENTS†	NORMOTENSIVE PATIENTS	NONRESPONSIVE PATIENTS
City-County Clinic	32	26	4	10	32	23	4	13
Veterans Administration Hospital*	43	33	21	6	43	34	24	5
Totals in group	75 (100%)	59 (79%)‡	25 (33%)	16 (21%)	75 (100%)	57 (76%)§	28 (37%)	18 (24%)

*Includes 7 private patients.
†Reduction in mean blood pressure of 20 mm. Hg. or more.
‡12 unresponsive to Rauwolfia & hexamethonium.
§10 unresponsive to Rauwolfia & pentolinium.

Group 2

This group consisted of 34 patients who received Rauwolfia and pentolinium from the beginning of combination therapy. Clinical data are summarized in Table 1, and results of therapy in Table 4. Thirty-two, or 94 per cent, were responsive to treatment, and 14, or 41 per cent, became normotensive. Seven of these patients, including the 2 who were unresponsive, had previously received Rauwolfia alone. Side effects are summarized in Table 5.

TABLE 3. *Comparative Frequency of Side Effects with Rauwolfia Combined with Pentolinium or Hexamethonium.*

SIDE EFFECT	RAUWOLFIA & PENTOLINIUM*		RAUWOLFIA & HEXAMETHONIUM*	
	NO. OF CASES	PERCENTAGE†	NO. OF CASES	PERCENTAGE†
Bradycardia	50	67	51	68
Nasal congestion	38	51	46	61
Sedation	29	39	20	27
Increased appetite	24	32	16	21
Weight gain	26	35	15	20
Dizziness	30	40	26	35
Syncope	1	1	4	5
Constipation	37	49	39	52
Anxiety & depression	3	4	2	3

*75 patients in group.
†Percentage of total number of patients receiving drug combination.

DISCUSSION

Until the pathologic physiology of hypertension is more adequately understood and can be specifically reversed, there appears to be a theoretical and practical advantage to treating hypertension with a mild centrally acting agent such as Rauwolfia and adding a ganglionic-blocking agent if additional therapy is necessary. With this approach, patients with mild hypertension who are responsive to Rauwolfia alone,

TABLE 4. *Blood-Pressure Response* to Rauwolfia Combined with Pentolinium from the Outset of Therapy.*

SOURCE OF DATA	RESPONSIVE PATIENTS†	NORMOTENSIVE PATIENTS	NONRESPONSIVE PATIENTS	NO. TREATED
City-County Clinic	26	10	2	28
Veterans Administration Hospital	6	4	0	6
Totals	32 (94%)	14 (41%)	2 (6%)	34 (100%)

*In upright position.
†Reduction in mean blood pressure of 20 mm. Hg. or more.

TABLE 5. *Side Effects in Patients Receiving Rauwolfia Combined with Pentolinium from the Outset of Therapy.**

SIDE EFFECT	NO. OF CASES	PERCENTAGE
Bradycardia	14	41
Nasal congestion	20	59
Sedation	11	32
Increased appetite	9	26
Dizziness	14	41
Syncope	2	6
Weakness	20	59
Blurred vision	11	32
Constipation	17	50

*Total of 34 patients.

will not be subjected to more intensive therapy. The blood-pressure reduction with Rauwolfia in combination with ganglionic blockade is orthostatic and may be corrected, if excessive, if the patient lies down. The responsiveness to nor-epinephrine is not lost as it is with adrenergic blockade so that excessive hypotension may be readily and effectively combated. The Rauwolfia, by virtue of its additive effect to ganglionic blockade, permits a lower dosage of the ganglionic-blocking agent and thereby reduces the untoward effects attending the use of any ganglionic-blocking agent.

Practically, it has been shown that Rauwolfia combined with ganglionic blockade is effective in reducing the blood pressure in the majority of patients in whom it has been used. Theoretically, if the degree of ganglionic blockade depends on dosage of the blocking agent, the only limitation to producing any degree of blood-pressure reduction that one desires should be the development of prohibitive side effects of the ganglionic blockade. Clinical experience suggests that this is a reasonable assumption.

It is, of course, not possible, in view of the similar pharmacology of the sympathetic and parasympathetic ganglions, specifically to block the sympathetic ganglions while the parasympathetic ganglions are not affected. Many of the side effects of ganglionic blockade are related to blockade of parasympathetic ganglions. One then desires an agent that will have a more regular and prolonged effect so that the reduction in blood pressure will be smoother and perhaps the orthostatic dizziness and fainting minimized. Such an agent, although affecting the parasympathetic ganglions, should permit better adjustment of the organism with less marked gastrointestinal and bladder symptoms. Previous reports of Smirk[3] and Freis et al.[2] suggest that pentolinium possesses a more prolonged and even ganglionic blockade than hexamethonium and that it is in fact associated with fewer untoward effects.

The series of patients described here who first received Rauwolfia and hexamethonium, and later Rauwolfia and pentolinium, support the impression that a majority of patients can be expected to respond to this form of therapy. The comparable response and normotensive rates indicate the similarity of effect between hexamethonium and pentolinium. The average daily dose of hexamethonium for all patients who were responsive was 2307 mg. in comparison to an average daily dose of 341 mg. of pentolinium, suggesting that milligram for milligram pentolinium is six or seven times more potent than hexamethonium.

Untoward effects attributable to Rauwolfia such as bradycardia, nasal congestion, increased appetite, weight gain and sedation were similar in the pentolinium and hexamethonium periods. Dizziness on standing and constipation are associated with ganglionic blockade, regardless of type, and were present in comparable numbers. The intensity of these effects was frequently less with Rauwolfia in combination with pentolinium.

Summary

One hundred and nine patients received Rauwolfia and pentolinium together in the outpatient treatment of hypertension. Ninety-one, or 83 per cent, responded to treatment with a reduction of 20 mm. of mercury or more in the mean arterial pressure, taken in the upright position. Thirty-nine, or 36 per cent, were normotensive in the upright position.

Seventy-five patients received Rauwolfia combined with hexamethonium for three months or more and were then shifted to Rauwolfia combined with pentolinium. Fifty-seven, or 76 per cent, were responsive to the former, and 59, or 79 per cent, to the latter combination.

Untoward side effects, attributable to ganglionic blockade, were similar in frequency but less intense with Rauwolfia in combination with pentolinium.

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MEDICAL PROGRESS

POTASSIUM AND THE KIDNEY*

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DURING the last decade major advances have been made in the understanding of the metabolism of potassium and the role of this ion in a variety of pathologic states. Several excellent reviews on various aspects of this subject have appeared in the past few years,[1-4] but none have been concerned primarily with the relation of potassium and the kidney. In this field recent investigation has been particularly fruitful, and it now seems appropriate to review the problem in an attempt to integrate earlier work with current knowledge.

The body of this paper is devoted to a consideration of the excretion and conservation of potassium by the normal and diseased kidney, as well as to brief discussions of factors modifying renal handling of potassium, the relation of potassium excretion to acid-base regulation and the effects of potassium depletion on the kidney. Attention is given chiefly to studies in man, but occasional reference is made to certain experiments in animals that elucidate fundamental mechanisms.

EXCRETION OF POTASSIUM BY THE NORMAL KIDNEY

Changes in renal excretion of potassium constitute an important defense against excessive retention or loss of this ion, but the factors normally determining the rate of potassium excretion remain undefined. It was suggested earlier that the serum potassium concentration and the amount of potassium being filtered at the glomerulus might play a major part in regulating potassium excretion.[5] It now appears far more likely that the potassium content of cells, either body cells in general or cells of the renal tubules in particular, is the critical factor in regulating potassium excretion and conservation.[2,6] This opinion is based chiefly on the observation that wide variations in potassium excretion occur independently of plasma potassium concentration or filtered load.[2,6]

A fundamental addition to the knowledge of potassium excretion has been provided by the demonstration that more potassium may be found in the urine than is simultaneously filtered at the glomerulus.[7,8] This indicates that potassium must be secreted by the renal tubules. The secretion of potassium apparently is accomplished by an ion-exchange mechanism in which potassium of the tubular cells is exchanged for the sodium of the glomerular filtrate.[6] Such a mechanism is analogous to the hydrogen sodium exchange between tubular cells and intraluminal fluid.[9] Although the data on potassium secretion have been obtained chiefly in animal experiments under special circumstances potassium secretion has also been demonstrated in normal man.[6]

It has been proposed that potassium secretion by ion exchange is a more or less continuous process that may account for essentially all the potassium appearing in the urine.[10,11] Recent micropuncture studies in animals show that the potassium concentration in fluid collected from the middle third of the proximal tubule is lower than that in the plasma.[12] If active reabsorption of potassium continues to completion in the remainder of the proximal tubule distal secretion would have to account for all excreted potassium.

The first observation of the ability of the organism to deal with large quantities of potassium was made in 1871, when it was noted that a normal man could rapidly ingest as much as 10.5 gm. (140 milliequiv.) of potassium chloride without untoward effects.[13] It was also pointed out that persons subsisting largely on potatoes apparently suffered no ill effects from a daily intake of 20 to 40 gm. (500 to 1000 milliequiv.) of potassium and thus presumably excreted this amount without difficulty. Recent studies have provided a more quantitative description of the renal and the extrarenal effects of potassium loading. Under basal condition normal human beings usually excrete an amount of potassium equal to about 10 per cent of the quantity in the filtrate. When a load of potassium is administered orally to normal subjects, either as potassium chloride or as potassium bicarbonate, there is a rapid increase in potassium excretion, which reaches a peak in two or three hours.[14,15] At the time of maximal excretion an amount equal to 40 to 50 per cent of the filtered potassium appears in the urine.[14,15] With administration of single doses larger than 0.5 milliequiv. per kilogram of body weight renal excretion is usually insufficient to prevent a rise in serum potassium concentration.[14-16] Doses of approximately 1 milliequiv. of potassium per kilogram increase serum potassium concentration by as much as 1 milliequiv. per liter and after

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doses of 2 to 2.5 milliequiv. per kilogram potassium concentration usually reaches 6 to 8 milliequiv. per liter.[14-16] Electrocardiograms show slight to marked elevation in the height of the T waves, roughly proportional to the rise in serum potassium concentration. Within four or five hours of potassium loading serum concentration and urine potassium excretion have generally returned to normal or nearly normal values.[14-16]

Much larger doses of potassium have been given to normal subjects over several hours, and, although no biochemical data are available, it appears from the clinical description that symptoms of severe potassium intoxication developed in these cases.[19,20] After ingestion of 5 milliequiv. of potassium per kilogram of body weight in one to three hours profound muscular weakness, ataxia and prostration occurred, and it seems probable that serum potassium concentrations were greatly elevated.

The only reported study on tolerance to intravenous administration of potassium in a human subject showed that the administration of 113 milliequiv. (approximately 1.5 milliequiv. per kilogram of body weight) in an hour resulted in a rapid increase in potassium excretion comparable to that in subjects given a similar oral load.[14] Serum potassium increased by 1 milliequiv. per liter. The available data concerning the effects of potassium excess on renal function are limited to a study in which 7 subjects were given by mouth 2.5 milliequiv. of potassium per kilogram of body weight.[14] There were no significant changes in glomerular filtration rate in 5 of these subjects, but in 2 there were abrupt falls of about 30 per cent in the inulin and urea clearances. There was no evidence of circulatory collapse, and the mechanism through which the glomerular filtration rate was reduced is not evident.

In summary it appears that rapid oral administration of potassium in amounts up to 1.0 milliequiv. per kilogram of body weight produces only a slight rise in the serum potassium concentration, but that the administration of large doses of potassium (2.5 milliequiv. per kilogram) will sharply elevate serum potassium concentration. The latter finding suggests that potassium may in fact be ingested and retained in quantities sufficient to prove hazardous, even in the presence of normal kidney function. This observation is in contrast to the earlier opinion that potassium could not be taken orally in sufficient quantities to produce intoxication because of gastric intolerance.[15] On the other hand daily amounts in excess of 5 milliequiv. per kilogram of body weight have been administered in divided doses over prolonged periods without untoward effects. Up to 640 milliequiv. of potassium chloride has been administered daily to a patient with acromegaly, without ill effects,[21] and patients with myasthenia gravis have ingested approximately 500 milliequiv. of potassium daily for weeks or months, without evidence of intoxication.[22]

Although the kidney plays a vital part in defending against acute potassium intoxication it should be emphasized that the tissues are also of great importance. Most of the potassium retained after an oral or intravenous load leaves the extracellular space.[23,24] The transfer to tissues, possibly by an ion-exchange process, has the effect of sequestering potassium in areas where significant toxicity does not seem to occcur. This mechanism protects the organism from a lethal accumulation of potassium in the plasma. Subsequently, as potassium is removed from the extracellular fluid by the kidney, the excess tissue potassium is probably gradually mobilized and excreted.

It is of special interest that continued administration of potassium produces a striking increase in the tolerance of the organism to this cation. A dose of potassium that is almost uniformly fatal to an animal becomes innocuous after several days of sublethal loading by mouth or intraperitoneally.[25] Increased tolerance to potassium loads may persist for a week or longer after potassium administration has been discontinued.[25] Although some experimental studies indicate that slightly increased tolerance can be produced by previous administration of DOCA or adrenocortical extract[26] such protection is very small in comparison to that afforded by prolonged potassium loading.[25] It is not known whether prolonged administration of potassium potentiates tissue uptake, but it has been demonstrated that this maneuver greatly increases the efficiency of the renal excretion of potassium loads.[8] As a result the urinary excretion of potassium usually exceeds the filtered load. This secretion of potassium is probably partly responsible for preventing the rise in serum potassium that is seen in unadapted animals. The demonstration of potassium secretion is not facilitated by previous administration of DOCA but only by previous loading.[6]

Excretion of Potassium by the Diseased Kidney

In acute renal failure accumulation of potassium in the extracellular fluid is a common finding.[27] In the anuric patient, even if there is no intake of potassium, tissue catabolism releases potassium from the cells where the concentration of this cation is roughly thirty times that of the plasma. A large amount of this potassium is probably sequestered in normal tissues, but, without removal of potassium by the kidney, the serum concentration may reach lethal levels. This is particularly true when inadequate caloric intake, hemolysis, fever or trauma increases tissue destruction. Occasionally, with proper management of nutrition and in the absence of important

complications, serum potassium may remain normal or only slightly elevated throughout the anuric phase despite progressive azotemia.[27]

There is considerable disagreement concerning the frequency of hyperkalemia in patients with severe chronic uremia (nonprotein nitrogen or blood urea nitrogen above 100 mg. per 100 cc.). Some of the early investigators of this problem found elevations of potassium concentration frequently,[28,29] and others noted it very uncommonly.[30-32] Various methods were employed in the chemical measurements, and only a small number of patients were studied in any single series. More recent studies indicate that spontaneous elevations of serum potassium concentration to levels above 5.5 milliequiv. per liter occur in approximately half the patients with severe azotemia.[33-35] Elevations above 6.5 or 7.0 milliequiv. are uncommon and usually occur only when severe oliguria (urine volume less than 250 cc. per day) supervenes as a final event in the patient's course.[34] In seven years at the Mayo Clinic only 13 patients with chronic renal disease were seen whose serum potassium levels were above 7.5 milliequiv. per liter, and these were in the last stages of uremia.[36] Although oliguria is ordinarily a prerequisite for severe hyperkalemia it is not always accompanied by marked elevations in serum potassium concentration.[34] It appears that spontaneous hyperkalemia of a sufficient degree to cause death occurs only in association with a general deterioration of renal function and in the terminal phase of chronic renal insufficiency.

The existence of a normal or only slightly elevated serum potassium concentration in most patients with chronic uremia clearly implies that potassium excretion proceeds at a normal rate despite marked reductions in the potassium filtered at the glomerulus. Therefore, the ratio of excreted to filtered potassium is high,[15] and, on occasion, the excreted form has been observed to exceed the filtered.[37] Although this evidence strongly suggests that potassium secretion occurs in these patients the error in estimating very low filtration rates is so great as to prevent a definite conclusion. Nevertheless, it seems clear that the ability of the damaged kidney to excrete normal amounts of potassium despite great reductions in functioning renal mass constitutes a kind of adaptation. It is not unreasonable to suppose that the mechanism by which this is achieved is similar to that which produces renal adaptation in normal, potassium-loaded animals.[8]

Although the diseased kidney can adapt itself to the usual daily intake of potassium its response to an acute oral load of this ion is abnormal. In patients with renal failure due to a variety of kidney diseases potassium excretion increases at a much slower rate than in control subjects.[15,38] In a group of patients in renal failure, three hours after the administration of approximately 1 milliequiv. per kilogram of body weight, only 4 to 39 per cent of the potassium had appeared in the urine, in contrast to an excretion of 49 to 100 per cent during the same interval by normal subjects.[38] Serum concentration of potassium rose 1.5 to 3.5 milliequiv. and, in some cases, to 8 or 9 milliequiv. per liter, resulting in electrocardiographic signs of intoxication.[15,38] The elevated serum potassium concentration often persisted for many hours longer than it did in the controls. Calculation of the distribution of the retained potassium again indicates, as in the normal subjects, that most of the potassium had been sequestered in nonextracellular sites. The data demonstrate that relatively small amounts of potassium given as a single dose to a patient with renal insufficiency may produce dangerous elevations of serum concentration, although larger amounts than this have been added to the daily diet in divided doses without untoward effects.[39] An interesting conclusion that can be drawn from the studies of both normal subjects and those with renal disease is that on many occasions concentrations of 8 milliequiv. per liter or more can be reached without serious clinical consequences.

Conservation of Potassium by the Normal Kidney

The normal kidney is so extraordinarily efficient in conserving sodium that in approximately five days after a subject is placed on a virtually sodium free intake, urinary excretion declines to a few milliequivalents daily.[40] By contrast, conservation of potassium after withdrawal of this element is relatively inefficient. The institution of a diet very low in potassium is difficult, and only in the last several years have data on the renal response to low potassium intake become available.[41-44] The diets recently employed have generally contained 10 to 15 milliequiv. of potassium per day. After a week on such a regimen urinary potassium excretion of normal subjects fell to approximately 20 to 25 milliequiv. per day.[42-44] In two weeks the urinary excretion was practically equal to the intake (10-15 milliequiv. per day),[42-44] but additional small stool losses resulted in a slightly negative potassium balance. In 1 patient studied for a prolonged period, there was a calculated negative balance of 1 or 2 milliequiv. per day from the sixteenth to the fifty-fifth and last day of observation.[44] However, in view of the inherent limitations in the precision of balance technic, it is difficult to be certain that equilibrium had not been achieved. The total potassium deficit in each of these studies ranged between 250 and 300 milliequiv., representing approximately 8 to 10 per cent of the initial normal body potassium. Serum potassium usually fell to approximately 3 milliequiv. per liter, and serum bicarbonate rose slightly. Few,

if any, clinical abnormalities were noted, although it is of interest that a loss of potassium of this magnitude is one to which clinical significance has commonly been attributed.

In a recent study, a diet containing 1 or 2 milliequiv. of potassium per day was employed.[45] After a week urinary excretion fell to between 15 and 30 milliequiv. per day. Restriction of sodium as well as potassium appeared to augment the efficiency of the renal conservation of potassium.

With more prolonged periods of potassium deprivation in pathologic states or with more severe deficits induced acutely, much lower urinary potassium excretions have been noted. After sixteen days of potassium depletion with an ion-exchange resin and total losses of 400 to 800 milliequiv. urinary excretion has been observed to drop as low as 3 to 5 milliequiv. per twenty-four hours.[46] Comparably low levels have been observed during the recovery period from diabetic acidosis,[47] during protracted vomiting[48] and in chronic diarrhea.[49] In such patients urinary potassium concentrations below those found simultaneously in the plasma are occasionally encountered.[48,49]

These observations indicate that determination of urinary potassium excretion may be useful clinically as an index of the severity and duration of potassium depletion. If excretion is less than 10 milliequiv. per twenty-four hours one can assume that chronic potassium depletion exists, even though serum potassium concentration is not greatly lowered. Analyses of random specimens of urine may yield similar information if concentrations are less than 10 milliequiv. per liter and if it is known that the urine volume is not more than 1 to 1.5 liters per day. A finding of a low urinary potassium is also useful in that it virtually excludes impaired renal conservation as the cause of the potassium loss.

Although low intake of potassium and sluggish initial renal conservation are important factors in producing depletion, severe potassium deficiency in most cases results only when there are also substantial extrarenal losses or unusual factors promoting increased renal excretion of potassium (for example, diabetic acidosis and adrenocortical hyperfunction).

Conservation of Potassium by the Diseased Kidney

In most patients with advanced renal insufficiency concern about disturbed potassium metabolism is directed to the problem of potassium accumulation, but on infrequent occasions, hypokalemia may occur. Potassium deficiency in such patients is usually associated with both inadequate intake and extrarenal losses from vomiting or diarrhea.[34,50] Under these circumstances, even in the absence of renal disease, potassium depletion may be expected, and it is not necessary to postulate any defect in renal conservation. A review of the literature has not revealed any case of demonstrated renal potassium wasting in a severely azotemic patient. Renal potassium wasting has been reported only in patients in whom damage to the tubules was far more prominent than glomerular involvement. This group includes patients with so-called "renal tubular acidosis" and Fanconi's syndrome, those in the diuretic phase of acute renal insufficiency and a small additional group including patients with an excessive production of aldosterone.

In patients with "renal tubular acidosis" the potassium loss as well as the calcium loss and osteomalacia have been attributed to defective acidifying mechanisms.[51] These patients tend regularly to excrete urine of pH 5.5 or higher despite the presence of hyperchloremic acidosis, and they have a limited ability to excrete titratable acid and ammonium.[51] It has been postulated that the potassium and calcium losses represent a response to the demand for urinary cation when ammonium and titratable acid cannot meet this need.[51] Although the absence of appreciable glomerular disease has been emphasized recent measurements indicate significant reductions in glomerular filtration rate in many cases.[52,53] The clearance data suggest diffuse renal impairment in which the glomeruli, at least in the initial stages, are simply less seriously involved than the tubules.[52] Several patients with this syndrome have later become moderately azotemic.[54] There is at present a paucity of pathological data in patients with "renal tubular acidosis."[53] It is thus impossible to say whether they have a single underlying disease or whether they are a pathologically heterogeneous group who have in common only severe tubular dysfunction, one manifestation of which is potassium wasting.

Many cases of hypokalemia and potassium wasting have also been observed in Fanconi's syndrome.[55-57] It is thought that the cation wasting in these patients is secondary to the increased excretion of organic acids.[51] If the potassium loss in "renal tubular acidosis" and Fanconi's syndrome is simply due to a general defect in cation conservation by the kidney, it is somewhat surprising that sodium depletion has not been a prominent associated feature.[53,55] Further study will be necessary to elucidate fully the mechanism of the potassium loss.

A small group of patients with renal disease and potassium wasting have been reported[58-63] who are not easily fitted into any of the classifications mentioned above.* They had isosthenuria, normal or borderline elevations of the blood nonprotein nitro-

*Three patients originally described as cases of potassium wasting due to chronic nephritis[64] are not included here since they all had hyperchloremic acidosis and have since been reclassified by Albright and Reifenstein[51] as cases of "renal tubular acidosis."

gen, moderate reductions in glomerular filtration rate and, in most cases, greatly elevated serum bicarbonate concentrations. These patients failed to conserve potassium on usual intakes despite severe hypokalemia, and potassium retention was achieved only with administraton of large potassium supplements. In several cases excessive production of aldosterone by an adrenocortical tumor has been implicated as the cause of the potassium wasting. Increased amounts of aldosterone were found in the urine, and removal of the tumor corrected the electrolyte disturbance.[62,63] It thus appears that adrenal tumors have been responsible for at least some of the cases of unexplained renal potassium wasting. On the other hand autopsy examination of a patient with a potassium-wasting defect revealed only malignant nephrosclerosis, the adrenal glands being entirely normal.[59] Although the finding of histologically normal adrenal glands does not exclude adrenal overproduction of aldosterone the possibility remains that this patient (and perhaps some of the others) represented an example of primary renal potassium wasting. When one considers that potassium wasting occurs as one of multiple tubular disorders in "renal tubular acidosis" and Fanconi's syndrome it seems likely that potassium wasting occasionally develops as an isolated disturbance in primary renal disease.

During the diuretic phase of acute renal insufficiency the damaged tubules are unable to conserve electrolytes and water properly. As a result, potassium, as well as other cations, may be lost in significant amounts.[65] Observers have noted that the serum potassium may occasionally fall to levels below 3 milliequiv. per liter.[65,66] No cases of death from potassium deficiency have been reported in this stage.

Extrarenal Factors Influencing the Renal Excretion of Potassium

Thus far discussion has been largely concerned with renal factors that modify potassium excretion. In a variety of physiologic and pathologic states potassium excretion by the kidney is altered as a result of extrarenal factors, some of which are mentioned briefly below.

Adrenal hormones (cortisone, compound F and aldosterone), as well as desoxycorticosterone, accelerate potassium excretion and produce a negative potassium balance. This increased excretion of potassium appears to depend on increased renal sodium reabsorption and is probably associated with an exchange of sodium and potassium ions between the tubular cell and the intraluminal fluid.[67-69] Restriction of sodium intake minimizes or prevents the potassium loss,[67,69] presumably by depriving the tubules of extra sodium that may be exchanged for potassium.

Potassium excretion is increased whenever there is a strong stimulus to retain sodium and at the same time a requirement for cation excretion exists. Thus, in each of the following circumstances in which these requisites are satisfied, a large potassium diuresis ordinarily results: during the administration of sodium paraminohippurate[70] or sodium sulfate[71] to subjects ingesting a low-sodium diet or receiving ACTH or cortisone; after the administration of ammonium chloride,[72] mercurial diuretics[73,74] or a carbonic anhydrase inhibitor[75,76] to patients with cirrhosis or severe congestive heart failure; and after the infusion of sodium paraminohippurate loads in nephrotic patients.[77] On the other hand prior potassium depletion curtails the potassium diuresis that normally occurs in response to a variety of stimuli, including hyperventilation, loading with alkali and the administration of a carbonic anhydrase inhibitor.[78]

Potassium excretion varies in a predictable fashion during a twenty-four-hour period.[79,80] As with sodium and chloride there is a distinct nocturnal suppression of potassium output that is not dependent on the temporal distribution of food intake,[79-82] posture[82] or changes in glomerular filtration rate.[81-83] Reversing or otherwise modifying the pattern of sleep and activity for periods up to several days does not consistently or significantly alter the rhythm.[82,84] Rhythmic changes in adrenocortical activity do not normally seem to regulate cyclic electrolyte excretion,[82,83] and no adequate explanation for the diurnal rhythm has yet been offered.

A variety of other factors affect potassium excretion. Sodium loads increase excretion of the ion.[85] Dehydration also accelerates potassium excretion,[86,87] possibly because of the increased intracellular potassium concentration after withdrawal of water from cells.

Water diuresis sometimes produces a slight, transient increase in potassium excretion.[88] In balance studies no significant change in twenty-four-hour potassium excretion occurs despite variation in volume of urine ranging from 1500 to 7000 cc. per day.[89] During water diuresis concentrations of potassium in the urine may fall below those in plasma.[90]

Potassium Excretion and Acid-Base Regulation

As noted above, under certain circumstances, some, if not all, of the potassium in the urine results from tubular secretion.[6,7,10,11] This addition of potassium to the glomerular filtrate is carried out by an ion-exchange mechanism in which sodium is reabsorbed in a manner analogous to hydrogen-sodium exchange.[9] The observation that potassium administration alkalinizes the urine[5,23,91] and that potassium-deficient, alkalotic patients often secrete an acid urine ("paradoxic aciduria")[92,93] first sug-

gested the possibility that potassium and hydrogen shared, and competed for, a common secretory mechanism.[11,94] In subsequent studies it was demonstrated that inhibition of hydrogen secretion with a specific carbonic anhydrase inhibitor increases potassium secretion, indicating that there is indeed a reciprocal relation between potassium and hydrogen secretion.[11,94] Thus, when there is a surplus of potassium in the tubular cells after potassium administration, hydrogen secretion is diminished and the urine becomes alkaline.[11,94] Conversely, when the renal tubules are depleted of potassium, hydrogen secretion is increased, and the urine becomes acid. This competition between potassium and hydrogen could explain the increased potassium excretion seen in both respiratory and metabolic alkalosis,[95,96] on the assumption that in each case a decrease in intracellular hydrogen-ion concentration permits increased potassium secretion. Similar competition between potassium and hydrogen may explain the reciprocal relation in the diurnal excretory rhythm of these ions.[97]

It was initially suggested that increased loss of hydrogen in the urine during the development of potassium depletion was responsible for the alkalosis of potassium deficiency,[11] but further studies have indicated that transfer of extracellular hydrogen ions to the tissues in exchange for intracellular potassium ions is primarily responsible for the initial elevation of plasma bicarbonate concentration.[98,99] Nevertheless, the kidney is ultimately responsible for the failure to correct the alkalosis, and the increased tubular hydrogen secretion plays an important role by increasing reabsorption of bicarbonate.[99] Thus, the urine in potassium-deficient, alkalotic patients is more acid and contains much less bicarbonate than one would expect in view of the elevation of bicarbonate concentration in the plasma.[99]

Metabolic acidosis regularly follows the administration of potassium chloride loads,[23,91] and rough calculations indicate that only about a third of the reduction in plasma bicarbonate concentration can be accounted for by the losses in the urine.[23,100] The disappearance of the other two thirds results from the transfer of potassium to cells,[23,100] either with equivalent amounts of bicarbonate or more likely by a potassium-hydrogen exchange in which extracellular bicarbonate is converted to carbonic acid.

In view of the effect of potassium depletion on renal regulation of acid-base balance it might be anticipated that reduced amounts of potassium would be demonstrable in the kidney of potassium-depleted animals. However, analyses of such renal tissues have failed to show this,[101] perhaps because of the difficulty in detecting a reduction in potassium content in the involved tubular cells, which may represent only a relatively small fraction of the entire kidney mass.

Potassium Depletion and Renal Disease

It has been known for some years that the kidneys of potassium-depleted animals undergo striking pathologic changes, characterized primarily by vacuolization and degeneration of the tubular epithelium, without changes in the glomeruli.[102,103] In several patients dying with potassium depletion as a result of chronic gastrointestinal losses similar lesions have been described,[104-106] and they have also been noted in patients with ulcerative colitis.[107,108] That disorders of renal function, as well as histologic lesions, may be produced by chronic potassium depletion is indicated by recent observations on a small group of patients severely depleted of potassium as the result of chronic diarrhea.[49,109] Some of these patients had slight albuminuria and cylindruria, but all were found to have isosthenuria and lowered glomerular filtration rates and renal plasma flow. Glomerular filtration rates were only moderately reduced, and none of the patients were frankly azotemic. The improvement in renal function that followed restoration of potassium deficits in some of these patients, and the absence of any other fluid, electrolyte or acid-base abnormality known to impair renal function, indicated that potassium depletion was specifically responsible for the defect. Renal biopsy in 2 patients revealed hydropic, degenerative changes in the proximal tubular epithelium quite similar to the lesions mentioned above.[109]

There is other evidence in the literature that potassium depletion impairs renal function. Reduced urea clearance, isosthenuria or polyuria has been noticed in a few patients with potassium depletion.[104,110,111] Polyuria regularly appears in potassium-depleted animals,[112,113] and a recent study suggests that glomerular filtration rate is reduced in potassium-deficient rats.[114] Direct evidence of disturbed tubular activity is afforded by the observation that the transport of paraminohippurate is inhibited in potassium-depleted kidney slices.[115]

The nephropathy of potassium depletion is probably most important as a complicating factor in circumstances in which renal function is already impaired. In patients with renal disease potassium depletion, occurring as the result of vomiting or diarrhea, may well lead to additional renal impairment. The azotemia commonly seen in patients with multiple electrolyte deficiencies after surgery may be the result not only of sodium depletion, dehydration and shock but also, possibly, of potassium depletion. Potassium depletion may be at least partly responsible for the changes in the renal function previously ascribed to alkalosis[116] since most of these patients are also depleted of potassium. It is also quite

probable that potassium depletion is the cause of the renal dysfunction in patients with adrenal tumors who are producing excessive quantities of aldosterone.[62,63] The clinical and physiologic implications of the renal disorder resulting from potassium depletion are discussed in more detail elsewhere.[117]

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MEDICAL INTELLIGENCE

ALCOHOL-INDUCED PAIN IN HODGKIN'S DISEASE*

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REPORTS by Verbeeten[1] and Bichel and Bastrup-Madsen[2] have called attention to the seldom reported phenomenon of the production of pain in Hodgkin's disease by ethyl alcohol. With the exception of an article by Hoster[3] this subject has not been discussed in the American literature. The phenomenon may appear before other signs of Hodgkin's disease and, consequently, may be helpful in diagnosis. For this reason and also because this effect of alcohol is unusual and interesting, we present a case and summarize the cases previously reported.

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CASE REPORT

A 20-year-old soldier first became ill with Hodgkin's disease in December, 1951. He was symptomatic from the time of apparent onset and had generalized disease at the time the diagnosis was proved by biopsy in May, 1952. Initially, he had peripheral lymphadenopathy, and hepatomegaly, splenomegaly and enlarged retroperitoneal nodes developed as the disease progressed. Pain was always a major problem. The most severe pain was located low in the back, but he also had pain in several bones. Repeated roentgenograms failed to demonstrate bone changes. He was treated with several courses of either roentgenotherapy or nitrogen mustard and finally with triethylene thiophosphoramide. Symptoms were always relieved, but remissions became progressively shorter, and he died in December, 1954. Since an autopsy was not performed the true extent of the disease remained unknown.

Early in the final hospital admission in April, 1954, it was difficult to keep him comfortable. He was continuously miserable, with pains, fever, weakness, anorexia and severe

depression. His physician decided to try intravenous injection of alcohol after only partial relief from many combinations of sedatives and narcotics. An intravenous infusion of a solution of 5 per cent alcohol and dextrose was started. Within a few minutes, after the patient had received only a small part of the 1000 cc. of solution, he began to have severe pain in several bones, especially in the lower legs. The pain was much worse than he had previously experienced. His physician was not immediately available to discontinue the infusion, and by the time it was discontinued the patient was in near collapse from pain.

Questioning brought out that he had been a fairly heavy drinker before his illness and during the first 2 years of his disease. At Christmas time in 1953 he found that a small amount of beer, less than 1 bottle, or a cocktail precipitated severe pain in the elbows, shoulders and several bones. This was so distressing that he became a total abstainer until the unfortunate incident described above.

Discussion

The case presented was typical of the phenomenon as described in the reports of Verbeeten,[1] Bichel and Bastrup-Madsen[2] and Petch[4] and in the discussion by Hoster[3] (Table 1). Very small amounts of the alcoholic beverage were required, sometimes only a mouthful. The pain appeared promptly even within one or two minutes in some cases, and pain was frequently felt at the site of demonstrable disease or where disease was demonstrated later. When the patient had spontaneous pain the alcohol-induced pain was usually more severe. Pain lasted for fifteen to sixty minutes and frequently was so severe that the patient abstained from alcohol thereafter. Although the experience was quite disturbing the patient often did not mention it to his physician until asked.

Alcohol-induced pain may precede any other recognizable manifestation of Hodgkin's disease by a year or more in some cases. Some of the patients who had pain from alcohol initially could tolerate alcohol after treatment of the Hodgkin disease. Bone disease was present in 8 of the 15 reported cases, and in 3 others, pain probably originated from mediastinal lymph nodes. Possibly, disease in a confined space is more likely to produce the phenomenon. Certainly, all patients with Hodgkin's disease do not experience pain after alcohol. Bichel and Bastrup-Madsen[2] reported the phenomenon in 9 of 62 cases, and it has been observed in patients with Hodgkin's disease but not in patients with other lymphomas.

Although pain was the most common effect of alcohol, Verbeeten[1] described generalized pruritus and a sense of constriction in the neck in 1 patient. One of the patients of Bichel and Bastrup-Madsen[2] experienced paresthesias. Hoster[3] observed an increase in pruritus and cough; he also noted that pain was replaced by local anesthesia if the alcohol intake was continued to a sufficient degree. The effect of alcohol on the over-all course of Hodgkin's disease is unknown. One of our patients, a man who did not experience pain from alcohol, repeatedly observed an increase in size of peripheral lymph nodes and fever after a night of heavy drinking and inadequate sleep.

Since the phenomenon has been observed after the intake of Dutch, Danish, English and American beer, ale, schnapps, wine, eggnog, cocktails and ethyl alcohol by mouth and by vein there is no doubt that the alcohol is the offending substance. The basis of this action is unknown. Bichel and Bastrup-Madsen[2] tested 7 vasodilators in some of their patients who had pain after alcohol. None of the vasodilators reproduced the pain.

Table 1. *Summary of Reported Cases.*

Source of Data	No. of Patients with Pain after Alcohol	No. of Patients with Pain from Alcohol before Diagnosis	No. of Patients with Proved or Probable Bone Disease	No. of Patients with Bone Pain	No. of Patients with Chest Pain from Mediastinal Lymph Nodes	No. of Patients with Symptoms from Alcohol besides Pain
Bichel & Bastrup-Madsen[2]	9	4	5	5	3	1*
Verbeeten[1]	4	3	2	2	0	1†
Petch[4]	1	1	0	0	0	0
Present series	1	0	1	1	0	0
Totals	15	8	8	8	3	2

*Paresthesias.
†Pruritus & sense of constriction in neck.

Conclusions

Some patients with Hodgkin's disease experience severe pain at the site of disease immediately after the intake of small amounts of beverage containing ethyl alcohol. This phenomenon may precede any other evidence of the disease and may disappear after therapy of the Hodgkin disease.

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BOTANY, required in the eighteenth-century medical curriculum, became a major avocation of many physicians. The first Sherardian Professor of Botany at Oxford was an eighteenth-century physician, and the Regius Professor of Botany at Paris in the early 1700's was a doctor of medicine.[1] The two most prominent physicians of the European continent of the eighteenth century — Boerhaave and Haller — made extensive and significant contributions to botany. To the physicians, William Withering, Erasmus Darwin and Jean Baptiste Lamarck, eighteenth-century botany also owed a debt. Carl Linnaeus, physician turned botanist, who named and described over 8000 plants, was the hub of the wheel of botany[2] in the century. Appointed to the chair of medicine at Upsala in 1741, he exchanged it the next year for the chair of botany. His followers sent him botanical specimens from many parts of the world. In colonial South Carolina, Dr. Alexander Garden, of Charleston, was his disciple.[3-6]

In the 1750's Garden, beginning the practice of medicine at Charleston, was an unhappy young man. Educated in Scotland and trained in medicine by botanists, he found much to lament about Carolina: "A horrid country, where there is not a living soul who knows the least iota of Natural History,"[7] "a climate so ill adapted to study,"[8] "A country abounding with almost every plant . . . yet . . . not . . . one botanist,"[9] "scarce one here that knows a cabbage-stock from a common dock — but when dressed in his plate, by his palate,"[10] "What has been passing in the literary world, is entirely unknown to us, in these regions, wholly, alas! separated from Europe."[11]

Garden found his pleasure in correspondence. In 1755, encouraged by mutual friends, he begged correspondence with Linnaeus. Four years later Linnaeus replied, setting Garden the task of collecting fish and reptiles. Although more interested in botany Garden carried out the assignment and sent many specimens preserved in rum on the hazardous journey to Sweden. Linnaeus approved of Garden's descriptions and gave his Carolina disciple carte blanche to send what he found of note. In Linnaeus's twelfth edition of *Systema Naturae* (1767) Garden is given credit for describing 3 new genera of plants, 2 new genera of fish and 60 new specimens of serpents, insects and fish.[8] Linnaeus obliged Garden by naming one of his plants after the Reverend Stephen Hales and another new genus after Dr. John Fothergill.

To honor his "happy illustrator of Nature of Carolina" Linnaeus named, in 1762, a spectacular ornamental shrub "Gardenia." The naming of the plant was a complex story.[12] Garden did not describe the plant. It was entirely fortuitous that Linnaeus chose to name it for one from a region where the plant was later to flourish. Introduced into England from the Cape of Good Hope, it was called Cape jasmine by a botanist friend of the importer. This name is still the popular name applied to the easily grown shrub of southern gardens — in distinction to the present hothouse-grown commercial gardenia. Other botanists were certain that it was not of the jasmine family. To prevent embarrassing his botanical friend, the importer requested Linnaeus, on declaring it "no jasamine," not to name it for him. By forfeit, Garden was honored.

Garden's major contributions to botany were in his early life. Later, he became thoroughly enmeshed in the successful practice of medicine.[13] In but one note did he admit any advantage of his colonial life over that of England. Referring to the Royal College of Physicians he wrote to his friend Ellis: "I would not forego the pleasure that I have in freedom, for all the gorgeous shackles of their jog-trot practice."[14]

Garden complained frequently of the exorbitant time his medical practice required.[15] Yet on many calls he was an excited observer of nature, and the experience described many years later by Frost[16] may have been a common one to Garden:

> The way a crow
> Shook down on me
> The dust of snow
> From a hemlock tree.
>
> Has given my heart
> A change of mood
> And saved some part
> Of a day I had rued.

Garden was a loyalist; his only son was a revolutionist. After the close of the war and the confiscation of his property, he moved to England. In the last ten years of his life, although in failing health and less interested than formerly in botany, he enjoyed in small measure his longed-for "sweet hours of converse"[17] with friends in and about London.

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 41401

PRESENTATION OF CASE

A sixteen-year-old boy was referred to this hospital because of headache.

Nine days previously he awoke with a severe, midline occipital headache, which was steady and nonradiating and was aggravated by motion of the neck, coughing, sneezing and straining at stools. The headache was not so severe on the next day. Seven days before admission he was able to play baseball; he noted, however, that co-ordination was not normal and that activity accentuated the headaches quite markedly. On the next day he complained of double vision, noting that one of the images was laterally and vertically displaced compared with the other, on looking to the left. The double vision became more constant on the next day, and the headache persisted. Four days before admission an ophthalmologist found no abnormality. Three days before admission he vomited shortly after awakening, during a period of increased intensity of the headache. Intermittent vomiting occurred during the next three days, each episode following a brief period of nausea. On the day of admission he entered another hospital. A lumbar puncture revealed pink spinal fluid under an initial pressure equivalent to 420 mm. of water, with a total protein of 28 mg. per 100 cc. The final pressure was equivalent to 220 mm. of water. The amount of fluid removed is not known. The headache was somewhat relieved during and after the procedure. The patient was then transferred to this hospital.

The family history and past history were noncontributory.

Physical examination revealed a well developed, well nourished, co-operative but drowsy youth. No abnormalities were found in the general physical examination.

The temperature was 98.6°F., the pulse 52, and the respirations 20. The blood pressure was 124 systolic, 60 diastolic.

Neurologic examination showed the patient to be oriented. He gave no evidence of intellectual impairment, although his responses to questions were slow and he appeared in moderate discomfort. The sense of smell was normal, according to the patient. Visual acuity and visual fields were normal. There was bilateral papilledema of 1 or 2 diopters. The pupils were 2.5 mm. in diameter and reacted to light and on convergence. There was no nystagmus. Grossly, the ocular movements were normal, but on red-glass testing there was a constant crossed diplopia on gaze to the left, with primarily a horizontal separation of the images. There was a questionably reduced corneal reflex on the left. Slight facial asymmetry was present, with minimal flattening of the right nasolabial fold. Hearing was normal. The ninth, tenth, eleventh and twelfth cranial nerves were normal. Finger-to-nose and heel-to-shin tests revealed slight unsteadiness bilaterally, and there was slight breakdown of movement in performance of rapid alternating movements of the hands. Tendon reflexes and abdominal reflexes were symmetrical and active. A bilateral Hoffmann response was present. The plantar reflexes were questionably extensor bilaterally. Sensory examination was entirely normal. There was moderate stiffness of the neck on flexion. The gait was normal.

The urine was clear and amber colored, had a specific gravity of 1.026 and gave a negative test for albumin and a green test, with sediment, for sugar; occasional white cells and red cells were found in the sediment. Examination of the blood revealed a hemoglobin of 16 gm. per 100 cc. and a white-cell count of 9400, with 84 per cent neutrophils, 8 per cent lymphocytes, 7 per cent monocytes and 1 per cent eosinophils. X-ray films of the skull showed the pineal to be calcified and in the midline (Fig. 1). The sella turcica was normal. There was no evidence of increased intracranial pressure.

On the day of admission a ventricular tap revealed increased pressure in both ventricles. The ventricular fluid contained 490 red cells and 20 lymphocytes per cubic millimeter. The total protein was 4 mg., and the sugar 83 mg. per 100 cc., and the chloride 124 milliequiv. per liter. The fasting blood sugar was 97 mg. per 100 cc. Re-examination on the evening of the same day showed the patient to be drowsy but co-operative. There was a marked impairment of visual acuity, the patient complaining of being unable to count fingers with either eye; there was fluctuation in severity of this visual loss, however. A ventriculogram, carried out later that evening, revealed no visualization of the fourth ventricle or aqueduct. The lateral ventricle and third ventricle, which was in the midline, were dilated. There was no deformity of the third ventricle. The posterior portion of the third ventricle was not visualized completely. A posterior-fossa exploration was carried out, revealing a normal-sized fourth ventricle in the normal position. There was no evidence of tumor.

A catheter was passed through the aqueduct into the third ventricle without difficulty. A tube was placed with one end in the right lateral ventricle and the other in the cisterna magna (Torkildsen procedure).

On the next day the patient complained of a severe, throbbing headache and vomited on one occasion. The headache was generalized. He was alert and co-operative. The only change in the neurologic

FIGURE 1. *Lateral Projection of the Pneumoencephalogram, Showing Symmetrical Hydrocephalus Due to Obstruction at the Mouth of the Aqueduct (Arrow).*
There is a large calcification in the region of the pineal gland.

examination was the presence of coarse horizontal nystagmus on left lateral gaze, and coarse vertical nystagmus on upward gaze. Later, he was observed to have coarse horizontal nystagmus on right lateral gaze also. Upward gaze was not possible beyond the horizontal level. The right eye was deviated slightly inward. He was able to count fingers. The plantar reflexes were of flexor type. A left ventricular tap was carried out, revealing a pressure equivalent to 260 mm. of water. Constant ventricular drainage was established. There was no significant change in the patient's condition during the next few days. It was noted that he was able to read small print during this time. Upward gaze was full. On the seventh hospital day he complained of severe, pounding headache, and about six hours later abruptly lapsed into coma, with episodic head retraction and extension of all four limbs. The pupils gradually changed in size from 2 mm. to 7 mm. They were unreactive to light. Ventricular fluid obtained from the left ventricle revealed 32,000 red cells and 58 neutrophils. There was marked fluctuation of blood pressure and pulse throughout this period. Approximately four hours after the onset of coma, respirations suddenly ceased. Artificial respiration in a respirator was of no value, and the pulse stopped about one and a half hours after cessation of respiration.

DIFFERENTIAL DIAGNOSIS

SIR GEOFFREY JEFFERSON*: This boy of sixteen, who had previously been well, suddenly was taken ill with headache and stiffness of the neck and died sixteen days after the first symptom appeared. The fact that the headache was aggravated by coughing and sneezing is not significant, for that is usual, but the fact that the headache was occipital is worth mentioning, for the average headaches are frontal, vertical or bitemporal. A severe occipital headache points to some trouble in the posterior part of the skull — something subtentorial. Whenever a patient, whatever his age, but particularly a child, has the onset of occipital headache and stiffness of the neck, two conditions, meningitis and blood in the cerebrospinal fluid, are suggested. The meningitis might be either influenzal or pneumococcal, for they start extremely abruptly and are fulminating. Blood in the cerebrospinal fluid acts just as blood in the peritoneum does — that is, it leads to reflex rigidity of the abdominal wall and stiffness of the neck muscles that is identical with the stiffness seen with acute inflammations. Against meningitis is the fact that the cerebrospinal fluid was pink. I am not told how many cells there were in that fluid.

After exploration of the posterior fossa, upward gaze was limited to the horizontal level. That is significant evidence of compression or damage at the level of the quadrigeminal plate on the roof of the aqueduct of Sylvius. Upward gaze is the most difficult movement for the eyes to make. Downward gaze is the easiest. Patients vary considerably in their ability to turn the eyes upward. This boy did not have ptosis; if he had, that would have been greater evidence of a lesion at the level of the quadrigeminal plate. A few days after the exploration upward gaze was full. It was too early for the ventricular Torkildsen procedure, which was carried out during the exploration, to have done any good. I am assuming that the Torkildsen tube was inserted because there was a block in the iter, which I believe the surgeons had disproved.

On the day that he died he had decerebrate fits. The level of decerebration, we know, physiologically is at the tentorium, so that brings me back to the roof of the aqueduct, the quadrigeminal plate. Episodic head retraction is characteristic of decerebration at the tentorial level. Decerebration can be brought about by a supratentorial lesion that causes severe tentorial coning, by an extradural hemorrhage from the middle meningeal artery and by a lesion of the posterior fossa, with which there can be the cerebellar rigid fits such as Hughlings Jackson[1] first described eighty years ago.

Another point is that co-ordination was not normal, as was proved when the patient played baseball, although that may have been due to the disturbance in vision, for later in the examination done in the

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hospital the co-ordination was not greatly abnormal. There were some cerebellar signs — not very many.

The fact that he vomited so much pointed strongly to a disturbance of the third ventricular nuclei or of those in the floor of the fourth ventricle. Vomiting is suggestive of infratentorial rather than of supratentorial lesions, especially if it is an early sign. I know from the procedure that was done that his physicians had the same thought.

I mentioned the pink fluid. I do not know how much blood there was in it, but there cannot have been a great deal if the fluid was only pink — if we all mean the same thing by pink. It is an important point that the total protein was only 28 mg. per 100 cc. That makes it unlikely that this boy had a tumor since the common tumor of childhood is a medulloblastoma, with which the protein is nearly always high, because the cerebrospinal fluid washes the surface of the tumor in the roof of the fourth ventricle.

The next finding to consider is the drowsiness. Can a patient have drowsiness with posterior-fossa tumor? Indeed he can, although it is not common. With brain tumors at the level of the tentorium there is a fairly well marked drop statistically in the occurrence of drowsiness; tumors above that level are much more likely to cause drowsiness. The drowsiness with tumors below the tentorium, we suppose, is due to a disturbance of the diffuse alerting system in the brain stem. The absence of papilledema is another point against a tumor that was doing any harm. This was not a patient who was suddenly taken ill and found to have had a "roaring" papilledema, the tumor having been silent for some time. The cerebellar and other signs add up to the likelihood that something was wrong underneath the tent or alternatively at about the tentorial level as a result of a lesion immediately superior to the tentorium.

I do not quite understand what the physicians meant when they said that there was no evidence of increased intracranial pressure and then later said that there was. I think I shall let that pass.

Then I come to an odd sign — that is, this boy could not count fingers with either eye for a short while and then he could count fingers again shortly after the operation. That inability could have been due to acute edema, but, to be quite honest, I do not understand that failure with its quick recovery. Whether that was the result of a choked disk or of pressure on the dorsal surface of the midbrain that was interfering with the lateral geniculate body, I do not know.

Will you comment on these pneumoencephalograms?

Dr. Joseph Hanelin: The pneumoencephalograms (Fig. 1) show a moderately severe internal hydrocephalus, which is symmetrical. The level of the obstruction appears to be at the origin of the aqueduct. In the course of our discussion of these films before operation, the question about the amount of pineal calcification came up. We also wondered whether there was an actual deformity of the posterior aspect of the third ventricle. Indeed, the pineal is fairly generous, although not above the upper limits of normal, and the level of the obstruction at the aqueduct is some distance removed from the pineal gland, which may indeed be enlarged.

Sir Geoffrey: A normal pituitary is what one would expect in a boy like that because craniopharyngiomas do not bleed or produce symptoms suddenly. We know that from Dr. Raymond D. Adams's[2] observations about pituitary apoplexy. I have never seen a case myself in a boy of this age, and I should think we could probably put that out.

There was radiologic evidence of a block at the tentorial level. What I have to do is to try to explain it on probabilities, because I do not think I am going to get farther than that. The fourth ventricle and the vermis were normal so that he did not have a tumor there. The only tumors that bleed much are those that have fragile vessels. The common tumor of childhood, the medulloblastoma, has fragile vessels, but does not usually bleed. It sometimes bleeds into itself but not into the cerebrospinal fluid to give rise to signs like those that this boy had. What we have just heard about the findings in the ventriculogram fits into what we know about intracranial tumors in childhood. Ingraham and Matson,[3] in their book, give the proportions of brain tumors above the tentorium in adults as about 75 per cent and only 25 per cent below, but in children the great majority are below. I do not think that this boy had a tumor — an astrocytoma or a medulloblastoma; I have never seen a tumor do this. Anyhow, a tumor was not found at operation. A glioblastoma has fragile vessels, but some difference in mass in the cerebellar exploration should have been noted. In the tumors in children Ingraham and Matson found about 9 hemangiomas in the cerebellum and about 90 astrocytomas. So hemangiomas of the cerebellum are uncommon; of course, in adults they are very common.

In an analysis that I made of 635 posterior-fossa tumors in 1953[4] 120 were astrocytomas, 84 were medulloblastomas, and 74 were hemangioblastomas. Hemangiomas do not usually bleed, but there is a type that does bleed — that is, the racemose arteriovenous malformation, which is very rare. In our group of 635 posterior-fossa lesions there were only 3 racemose arteriovenous aneurysms of the type with large vessels. Those 3 patients died suddenly from hemorrhage. This may have been an arteriovenous malformation that was not seen at operation, because such malformations are difficult to find unless a large vein containing arterial blood "tracking" across the surface is seen going into the lateral sinus or some other sinus. It is quite likely that he could have had one without the physicians' knowing it was present. Arteriovenous aneurysms occur on the cerebellum and on the brain stem. One type that has been ob-

served particularly in children is the posterior cerebral arteriovenous aneurysm draining into the vein of Galen. The aneurysmal varix (to give it its own title) in that situation would very perfectly produce these symptoms.

Was it an aneurysm itself? They are very rare in children under the age of sixteen. In over 300 that I have personally seen only 3 have been in children of sixteen years and under.

I should think that, on the basis of probabilities, the most unlikely condition is a tumor that bled. Since this boy clearly died of hemorrhage, from a lesion that burst into the lateral ventricles, I should think that the probability of an arteriovenous malformation somewhere about tentorial level, perhaps into the vein of Galen, which would explain the difficulties with the eye movements and vision, is the most likely. Less likely, statistically, but also less possible on the basis of the signs and the hydrocephalus, which I have to explain, is an aneurysm in another situation. I would put an angiomatous malformation, perhaps on the posterior cerebellar artery, causing block, as next less likely and tumor as least likely. I have eliminated infection, I hope correctly.

DR. BENJAMIN CASTLEMAN: Thank you very much, Sir Geoffrey.

Dr. Ayer, do you have any comments?

DR. JAMES B. AYER: My mind was running toward a ball-valve type of tumor, but that is out. They do not bleed as a rule. I suppose we can assume that this blood was not technical.

SIR GEOFFREY: We had an aneurysm in the aqueduct of Sylvius that did not bleed; it just blocked the aqueduct. When I saw that I wondered if it could really happen or whether I had been mistaken. Then, I went over to Sheffield and found that the pathologist there had an identical specimen with an aneurysm the size of a pea in the aqueduct of Sylvius.

DR. CASTLEMAN: Do we have any evidence that there was bleeding before the operation?

SIR GEOFFREY: I do not like to mention this; we do not have as much evidence as we should like to have. All there was was pink cerebrospinal fluid, which may, of course, have resulted from trauma. This may have been postoperative bleeding from the muscles of the neck, I suppose, for the surgeons did not mention having made cuts into the cerebellum. The removal of the pressure may have produced the burst of a vessel.

DR. WILLIAM H. SWEET: A difficult feature in the postoperative management after this patient went into coma on the seventh postoperative day arose from worry that he had a hematoma in the site that I had split in the vermis when I went forward beneath the tentorium up to the midbrain. The transitory paralysis of upward gaze, which did seem to be a clear-cut finding in the first postoperative morning and disappeared so promptly, I was rather inclined to attribute to local edema or trauma from the exploration so near the midbrain.

Before you comment on the findings may I ask one more question? Sir Geoffrey, you raised in a very genteel way a query whether or not it is worth while to put in a Torkildsen tube if one can easily pass a catheter through the aqueduct. My impression in the past has been this. When I have generously exposed the posterior fossa by the removal of a great deal of bone, a block in the aqueduct when that bone was intact may thereby have been eliminated; the cerebellum could move out into this open space, and the aqueduct open up. In this patient it was peculiarly easy to examine the posterior fossa — I could see around almost to the ventral midline of the pons and from each side forward to the fifth nerve. Hence, I thought it was a rather easy case in which to rule out external evidence of a vascular malformation. Nevertheless, in spite of finding no such evidence of a space-taking lesion in the posterior fossa, I thought I had better leave a Torkildsen tube in because I might have unblocked the aqueduct by my suboccipital craniotomy. Do you think that is not likely?

SIR GEOFFREY: I did not realize that I ought to have asked Dr. Sweet questions about the operation. I did not realize that was allowed.

DR. CASTLEMAN: You are permitted to do almost anything here.

SIR GEOFFREY: The cerebellum was freely mobile; you did not see anything there?

DR. SWEET: There was no evidence that I could see of a space-taking mass, or a vascular anomaly on the surface of the hemispheres or in the substance of the vermis.

SIR GEOFFREY: Of course, postoperative clots will produce symptoms like these. We have unfortunately had experiences with patients who died after a posterior-fossa exploration with four-limb rigidity. That condition is not recognized quickly enough to prevent the patient's death. How long after this boy showed signs of decerebrate fits did he die?

DR. SWEET: He was dead in four hours. If he had not been in such a precarious condition, I think I should have reopened the wound.

DR. CASTLEMAN: Should you like to suggest anything else, now, Sir Geoffrey?

SIR GEOFFREY: I am sure that I ought to. Dr. Ayer mentioned the question of a tumor somewhere. A colloid cyst or something of that sort, I think, is ruled out by the ventriculogram. This illness started with signs that could only have been caused by meningitis or hemorrhage; therefore, since it ended with hemorrhage, I think that I ought to stick to a vascular lesion. If that is completely wrong, it ought not to be!

I remember so well the days when I was teaching general surgery and had a patient with a swelling of the ankle. I asked one of the students what it was. He replied that he thought it was probably a psoas-

muscle abscess. So I said, "Ho, ho, ho, why would you think that?" "Well," he said, "it says in Treves's *Surgical Anatomy* that sometimes a psoas abscess tracks down and presents at the ankle." I think I had better stick to probabilities even though I am wrong.

DR. CASTLEMAN: Dr. Selverstone, do you have any comment?

DR. BERTRAM SELVERSTONE: I am unable to see the posterior part of the third ventricle well in the ventriculogram. It looks fairly large in proportion to the lateral ventricles in the anteroposterior view.

DR. HANELIN: The third ventricle is ballooned in a manner characteristic of a lesion either at the origin of the aqueduct or somewhere along its course. I should judge from the level of the obstruction that it was definitely close to the mouth of the aqueduct. The normality of the contour of the posterior part of the third ventricle is open to question. Before operation there was a question whether the impression upon the posterior aspect of the third ventricle in the region of the pineal gland was greater than normal. It was my impression that it was at most borderline; I could not be certain of a tumor in that area. Also, the pineal gland itself is some distance from the level of obstruction.

A PHYSICIAN: Dr. Hanelin, how often is the pineal gland calcified in a sixteen-year-old boy?

DR. HANELIN: Dr. Sweet just asked me that. I do not know what the statistics are. I think that, after the age of twenty or thereabouts, 50 per cent of pineal glands are visibly calcified. After the age of thirteen it is not uncommon to see some calcification. I think the amount of calcium in general is a function of age; more is laid down as the patients grow older. Some people never have much visible calcification within the pineal gland. Whether this amount of calcification is abnormal at sixteen years is questionable. There is a wide range of variation in the size of the pineal gland; some give it as 13 mm. in length and about 5 mm. in height. These measurements are in the upper limits of normal, the average being 5 to 8 mm. in length and about 3 or 4 mm. in height.

CLINICAL DIAGNOSIS

?Tumor of posterior fossa.

SIR GEOFFREY JEFFERSON'S DIAGNOSIS

Arteriovenous malformation at level of tentorium.

ANATOMICAL DIAGNOSES

Pinealoma, with compression of midbrain and obstructive hydrocephalus, ventricular hemorrhage and cerebellar pressure cone.

Pulmonary edema.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Dr. Adams will discuss the pathological findings.

DR. RAYMOND D. ADAMS: The final anatomical diagnoses were pinealoma, with compression on the midbrain, obstructive hydrocephalus, ventricular hemorrhage, cerebellar pressure cone and pulmonary edema. There were no other important pathological findings. At the time of autopsy the incision was well healed. There was some hemorrhage and edema in the adjacent skin. In the subdural space beneath the burr holes in the right occipital region there was a very small amount of blood. In the posterior fossa of the skull about 30 or 40 cc. of freshly clotted blood had accumulated. After the brain was removed, it

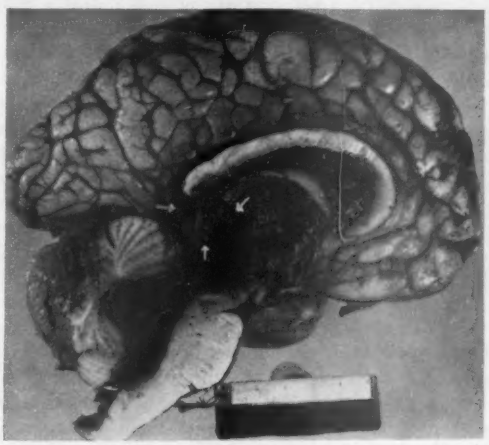

FIGURE 2. *Median Sagittal Section of the Brain, Showing Pinealoma (Arrows).*

was possible to see a hemorrhagic mass 2.0 cm. in diameter between the cerebellum and the splenium of the corpus callosum and the posterior surface of the midbrain. The brain weighed 1530 gm.; its surfaces were flattened. When sectioned sagittally in the midline, after formalin fixation, the ventricular system was found to be filled with an enormous mass of clotted blood. The aqueduct was enormously dilated. Blood had issued from the foramen of Magendie. In cutting through the aforementioned mass (Fig. 2), one could feel particles of calcium. It was very difficult to make out any discrete tumor tissue because of the heavy infiltration of blood. A microscopical section of a small piece of the hemorrhagic tissue showed that the calcified material, which was visible in the x-ray film, lay within the substance of the tumor and not in a normal pineal gland. This tumor was made up of fairly compact masses of large, oval, epithelioid cells, the nuclei of which were variable in size and chromatin density. Many of them had eosinophilic nucleoli, a feature that is fairly typical of the so-called pinealoma. The cells formed compact masses that were separated by strands of connective tissue. These strands were infiltrated by

small cells, probably lymphocytes, and imparted a mosaic appearance to the tumor tissue.

There are two or three points about this case that deserve further discussion. This tumor, as I have said, has been called a true pinealoma, according to the recommendation of Globus and Silbert.[5] These authors stated that tumors of this type tend to reproduce the fetal or embryonic pineal gland, which is made up of two types of cells: a large cell such as was present here and a small unidentified primitive cell. There are many objections to this particular theory of pinealoma, and these were pointed out by Dorothy Russell[6] a few years ago. In the first place the resemblance of these tumors to the fetal pineal gland is superficial at best, and the large cells with eosinophilic nucleoli are not seen in the fetal pineal gland; the small cells are not like the small cells in the undeveloped pineal, but are surely lymphocytes. Secondly, del Río Hortega[7] has pointed out that when silver carbonate and other stains are applied to the tumors, the cells do not take up the stain, which one might expect them to do if they were derived from the ependyma or had a common origin with the ependymal cells. Nor are there blepharoplastlike structures in their cytoplasm. Thirdly, tumors of exactly the same kind are found outside the pineal gland in the infundibular region, in the quadrigeminal plate, in the cerebellum and even in the mediastinum. Lastly, these tumors are almost exactly like the spheroidal-cell carcinomas of the testicle in that both contain remnants of other tissue elements — cartilage, bone and glands. I share the opinion of many pathologists that this is a teratoma of the pineal gland, one element of which has become malignant. This would explain the extreme radiosensitivity of the tumors, a property that is also characteristic of the closely related seminoma of the testicle and, Dr. Castleman tells me, of some teratomas of the mediastinum. It also explains the fact that many of these tumors have been associated with precocious sexual development in the male. Those who have written on the subject of dysgerminomas and seminomas point out the frequency with which hermaphroditism and pseudohermaphroditism has occurred in the female.

In attempting to correlate pathological findings with the symptoms I should stress the hemorrhage and the hydrocephalus. Surely, the headaches were due to one or the other of these conditions. The history suggests that the hemorrhage in this tumor antedated the operation. It may have caused the precipitous development of coma and the patient's death, as Sir Geoffrey has suggested. The unsteady gait could well be explained by downward pressure of the pinealoma on a superior cerebellar peduncle. It may have been the result of the hydrocephalus. The blurred vision and transitory blindness is not explained satisfactorily, nor has it been in other cases of hydrocephalus. Whether it represented an acute hydrocephalus with downward pressure on the floor of the third ventricle on the optic chiasm or whether there was pressure on the superior quadrigeminal plate and the lateral geniculate bodies or was due to acute compression of optic nerves by perineural hydrostatic pressure, I cannot say. It is unlikely that acute papilledema of such short duration could have caused such severe obscuration of vision. The limitation of upward gaze may have been due to the compression of the superior colliculus by the tumor or to the surgical procedure.

DR. SWEET: I wonder if we have made clear the spectacular decline in the patient's condition in the twenty-four hours before he was operated on. He had had good visual acuity and suddenly became almost blind. That was what led us to operate on him so soon after admission. It seems to me that the clinical history fits in rather well with the concept that he had at least three successive hemorrhages, the initial episode being abrupt in onset, with the midline occipital headache, the second, occurring in the hospital and leading to the sudden change in the visual acuity, and the third, which broke out of the confines of the pia and tissue surrounding the tumor and poured directly into the ventricles, again striking out of a clear sky on the seventh postoperative day while he was convalescing satisfactorily. I do not know whether or not one has the impression that we damaged the tumor at the time of the operation. The tentorium was between us and the base of the tumor.

DR. ADAMS: It is difficult to reconstruct these events from the pathology. The hemorrhage appeared fresh and not of three weeks' standing, but the recent bleeding was so extensive that it may have destroyed all such evidence of the original hemorrhage. I suppose the question will never be answered. One cannot say that the bleeding was postoperative because of the interval of seven days between operation and the last and fatal hemorrhage. Of course, the repeated tapping of the ventricles, with the reduction of pressure, could have started up the bleeding in a very highly cellular tumor with fragile vessels. I forgot to add that there were many subependymal hemorrhages such as we see after ventricular decompression. I should suppose that something like that happened rather than anything else.

DR. CASTLEMAN: At the time of operation, would you not have seen hemorrhage?

DR. SWEET: I should have seen hemorrhage in the aqueduct because I had a good view of it.

DR. CASTLEMAN: I meant in the tumor itself.

DR. SWEET: No; the tumor was on the top of the tentorium away from my view. The whole tentorium intervened between my field and the tumor.

DR. ADAMS: There were only a few hundred red cells in the ventricular fluid when the first ventriculogram was done. It is difficult to say whether that is the amount that may occur with any ventricular tap.

DR. HANELIN: Dr. Adams, do you suspect that as the result of the hemorrhage, the tumor became considerably larger than it was before the last episode of bleeding? Certainly, I should expect that ordinarily a 2-cm. mass of the pineal would be very clearly visible in the x-ray film. Ordinarily, a pinealoma is clearly visible in the ventriculogram, which in this case was quite satisfactory. The pineal mass is borderline; it may be slightly larger than normal, but it certainly does not begin to approximate a 2-cm. lesion.

DR. ADAMS: I cannot say; you may be correct in assuming that the tumor had been rapidly enlarged to about the size we found, and then had critically obstructed the outflow of cerebrospinal fluid and caused hydrocephalus. I must compliment Sir Geoffrey on his lucid discussion of the clinical data. More accurate diagnosis seems to be impossible from the data.

SIR GEOFFREY: The interesting point is that the lesion should have been in that area to produce those eye changes and the decerebration. It does do that beautifully so that the neurophysiology was worked out clinically more correctly. We had a woman who had fever after childbirth. The physicians "got her right" and sent her home in three weeks. A week after that she began having fits on the left side of the body that were nearly continuous. She recovered in two days, then suddenly became decerebrate and died within twenty-four hours. At postmortem examination she had thromboses of the veins over the cortex on the right side — the superior longitudinal sinus and the lateral sinus were completely thrombosed. The vein of Galen, too, was thrombosed, with thrombosis to the brain stem at the level of the quadrigeminal plate, and it was this last that had produced the decerebration. I was looking for a lesion at about the level of the classic decerebration that would produce that neurologic picture. That is what you have shown us. I have seen pinealomas metastasize all over the meninges, but I do not recollect one of these that bled in my own collection of more than 3000 brain tumors. This certainly was a highly instructive case, and I am obliged to Dr. Adams for his interesting discussion of the pathology.

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8. Bookplate of George Hayward, an editor of the *New England Journal of Medicine and Surgery* in its early years, professor of the principles of surgery and clinical surgery at Harvard Medical School and recording secretary and president of the Massachusetts Medical Society.

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INTERNATIONAL PROGRAM FOR WOMEN PHYSICIANS

NEARLY a century ago, during the darkest period of the Civil War, the New England Hospital was founded in Boston as the New England Hospital for Women and Children — by women and for the care and training of women. Probably the most inspired person in promoting the establishment of this unique institution was the Polish-born Dr. Marie Zakrzewska who was also instrumental in founding, with the pioneer Blackwell sisters, the New York Infirmary for Women and Children.

The expressed purposes of the New England Hospital, under the terms of its incorporation, were the advancement of women physicians, the medical care of women and the training of nurses. In the last respect it was truly a pioneer, for ten years after the founding of the hospital the country's first organized training school for nurses was established within its walls. Linda Richards, "America's First Trained Nurse," received her diploma here in 1873 and went on to the organization and direction of the training school at the Massachusetts General Hospital.

During the course of its many years of service the New England Hospital has tried to keep abreast of the times and still preserve its original purposes. In the maintenance of the most specialized of these — the advancement of women physicians — it remains one of a very small group in which the active-staff positions are held by women, men being included only on its courtesy and consulting staffs.

In line with this function there has now been established at the hospital a unique "International Educational Program," available to qualified women physicians from other countries and geared especially to their needs — social and economic as well as medical. These physicians, while benefiting from the various aspects of the training, will serve the New England Hospital in the capacity of house officers and contribute to the quality of its service to the community.

All applicants under the program must have a basic working knowledge of English, and all, except those from Canada and the British Isles, must have completed a year's internship in their own country. The application, including the applicant's medical-school curriculum, must be submitted to the Hospital before January 1 of any year for a twelve-month rotating internship to commence on July 1. Immediately preceding the internship a month's indoctrination and orientation period at the Hospital is required. This period includes an intensive course in English including medical terminology, a familiarization with drugs and medications and demonstrations of medical technics.

A thirty-six-week course in basic sciences and current advances in medicine is to be made part of the curriculum, and clinical conferences and field trips to outstanding local hospitals are in the planning.

On the economic side the medical staff of the hospital intends to offer ten scholarships up to a total of $5000 a year to improve the opportunity for participation in the program of all qualified applicants, regardless of economic status.

It is believed that by such a program the New England Hospital will help to demonstrate the value of democracy in education and make its own contribution to the progress of education on a world-wide basis.

GROUP HEALTH INSURANCE AT HARVARD

HARVARD University announces its own baby Blue Cross–Blue Shield health plan to go into effect for its 10,000 students next fall. Under the plan, according to a release from the University News Office, a single fee for all students will provide a comprehensive medical service, including infirmary and hospital care anywhere in this country or abroad.

An annual fee of $56.50 will cover the service, which can be continued through the summer vacation period for an additional five-dollar bill and extended to cover the student's family by the payment of additional premiums — $26.00 for a wife and $23.75 for the children, maternity benefits included. All special charges will be abolished, care of students admitted to local hospitals will be incorporated into the program, and increased facilities for dealing with emotional problems will be provided.

The plan is based on the one tried out at the Harvard Medical School, the School of Dental Medicine and the School of Public Health over the last two years, and the fee was established as a result of the experience with these graduate schools. The insurance features include hospital board and room at $17 a day up to a maximum of $1,000 per incident, a variable schedule of operating fees up to $300, a consultation fee of $25 for each illness if requested by the University Health Service and an allowance of $50 for medical services for an injury occurring outside of Metropolitan Boston.

STATE TUMOR DIAGNOSIS SERVICE IN NEW QUARTERS

FORTY years ago the knowledge of cancer was much more fragmentary than today and the criteria for its diagnosis were very poorly established. In 1912 the Harvard Cancer Commission recognized the difficulties and the poor diagnostic facilities that existed for the sufferers from cancer in the State. At that time, with the stimulus of Dr. John Collins Warren and the skill in pathology of Dr. E. E. Tyzzer, the Cancer Commission informally made available diagnostic pathological consultative services. By 1918 these services had proved so useful that a formal arrangement was made with the Massachusetts Department of Public Health, to establish, under the guidance of the Harvard Cancer Commission and in the Collis P. Huntington Memorial Hospital, a diagnosis service to which any physician in the State could send pathologic material for diagnosis in cases of suspected tumor.

This service proved to be increasingly valuable and popular, particularly to physicians without ready access to pathological facilities.

One incidental though valuable aspect of the Tumor Diagnosis Service has been that, as the worth of pathological diagnosis became appreciated in the field of cancer, the need for pathological diagnosis in other fields became apparent. In locality after locality the Service was increasingly utilized until the need for a full-time on-the-spot pathologist became appreciated, and a pathological laboratory was established. (This has happened again and again in areas of the State and is still happening.) However, the shortage of pathologists and the cost of establishing pathological laboratories, particularly in the smaller communities, made it difficult for such service to be widely available, and the need for the Tumor Diagnosis Service still exists.

There is no sure means of the diagnosis of cancer other than microscopical examination, and there is considerable evidence that this will continue to be so for many years to come. As suspicious lesions are detected earlier, the clinical diagnostic problems become more difficult and pathological diagnosis more essential.

During the past year over 1200 Massachusetts physicians used the Tumor Diagnosis Service. Because the Service almost entirely depends on postal facilities for transmission of specimens and reports, its operation other than in a key postal area entails added delay for patient and physician alike, so it has been desirable to maintain its activities in Boston.

For many years the Service has been guided by Dr. Shields Warren and Dr. Olive Gates through its migrations from the Huntington Hospital to the Harvard Medical School and from there to the Cancer Research Institute of the New England Deaconess Hospital. In July, 1955, the Harvard Cancer Commission delegated the responsibility for the operation of the Service to an experienced pathologist, Dr. John P. Ayer, with Dr. Gates and Dr. Warren remaining as consultants. On August 4 space became available at the Lemuel Shattuck Hospital, and the Service moved there, adding another contribution to the study of chronic disease that the Lemuel Shattuck Hospital renders to the Commonwealth.

It goes without saying that the Service in its new location will have continued success in providing diagnostic aid to citizens and physicians of the Commonwealth who require its help.

ANOTHER BLUE CROSS–BLUE SHIELD FIRST

Less than a year after announcing the pioneer Prolonged Illness Certificate, Blue Cross and Blue Shield, without any increase in subscription charges, have made effective another important innovation in the form of benefits for x-ray examinations and laboratory determinations undertaken on ambulatory patients in the physician's office, in the hospital outpatient department or in the hospital when the patient is admitted for diagnosis.

On the premise that a large percentage of diagnostic procedures can be covered in full because they are related directly to an unpredictable event, an unpleasant experience, or both, several broad classifications of events and conditions have been established for which "full credit" is extended for associated x-ray examinations and laboratory determinations. For the remainder, a generous "partial-credit" arrangement has been devised under which the patient pays a predetermined percentage of the total scheduled amount.

The addition of diagnostic coverage to their basic contracts and to their prolonged-illness contract now leaves Blue Cross and Blue Shield with only home and office calls for minor, nonsurgical services to consider. Whether or not such services should be covered is still debatable, but if they should be it is a safe guess that Blue Cross and Blue Shield in Massachusetts will find a satisfactory way to do it. A more detailed description of the new coverage will be found elsewhere in this issue of the *Journal*.

We alluded, in a late number, to the want of privies and urinals, so situated that the inhabitants of our crowded streets might avail themselves of them, instead of converting our highways into receptacles of filth, and endangering public morals, as well as health and comfort.

Boston M. & S. J., *Oct. 11, 1855*

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

Rupture of the Uterus, with Hemorrhage and Shock

A twenty-seven-year-old gravida V, para III, was admitted at term in early labor. She was obese and had had excessive weight gain with all three prior pregnancies, delivering babies weighing as much as 4.2 kg. and gaining 22.7 kg. with one pregnancy. She was Rh negative, with a rising titer of antibodies, but her weight rose only from 82.1 to 89.8 kg. in the current pregnancy and she experienced an otherwise uneventful course.

Admitted at 6 a.m. in early labor, she had intact membranes; no fetal heart beat was heard. However, preparations were made to tranfuse the baby, 1 liter of Rh-negative blood being on hand.

Twelve hours later the moderate crown presentation was observed, and after nitrous oxide, oxygen and ether anesthesia she was delivered by Ritgen's maneuver of a stillborn erythroblastotic infant weighing 5 kg. The shoulders were very large, and a great deal of suprafundic pressure was required for their delivery, which was accomplished with the posterior shoulder coming first and without intravaginal manipulation. The right mediolateral episiotomy did not extend, and although there was no excessive bleeding, an intravenous drip of oxytocin was started as a precautionary measure after immediate, spontaneous delivery of the placenta and secundines. The fundus appeared normal.

There had been 8 rapidly consecutive deliveries in the preceding hours at this hospital, with a consequent personnel shortage. In accordance with rules the patient was kept on the delivery table with a nurse guarding the fundus after delivery. The anesthetist's last record of blood pressure was 120 systolic, 80 diastolic, but there are no further notes until three hours later, when the patient returned to the ward in profound shock. It was nearly an hour more before blood was running, although the resident acted promptly and vigorously when notified. In his opinion she lapsed into shock shortly after delivery, but this was not recognized or called to his attention. Despite heroic efforts and multiple transfusions her condition deteriorated, and she died. Pelvic examination a few minutes before death revealed a large rupture of the lower uterine segment. Autopsy confirmed this and showed free blood in the abdomen.

This case was classified as a preventable death due to hemorrhage, shock and a ruptured uterus, all three of these items being avoidable.

Atony should be (and, in this case, was) suspected when excessively large fetuses are born particularly to multiparas, and this condition was admirably avoided. However, serious trauma to the birth canal should be just as assiduously suspected, and the uterus explored by an experienced operator. In the case under discussion such an examination would have saved the patient's life. Even without this, however, it is clear that she had been neglected during the three hours between delivery and the discovery of the profound shock. These three hours represent the last opportunity for saving her life, and although the physician in charge bore the responsibility, the hospital must accept some responsibility for not having notified him earlier of her condition. Absence of visible bleeding does not mean automatically a good pulse and blood pressure, even with a good fundus.

John Figgis Jewett, M.D.
Chairman

BLUE CROSS–BLUE SHIELD

COVERAGE OF DIAGNOSTIC SERVICES

THERE is a widespread belief that x-ray examinations and laboratory determinations undertaken on ambulatory patients are so subject to abuse that they cannot be covered effectively by a plan for medical or hospital care that uses the fee-for-service method of payment. Not convinced that this is true, representatives of Blue Cross and Blue Shield have worked for more than a year with the Blue Shield Fee Committee on Radiology, representatives of Blue Cross participating hospitals and others in an effort to evolve an approach that would accomplish the following:

Expand the scope of Blue Cross and Blue Shield coverage of x-ray examinations and laboratory determinations for patients who need such services but who are not sick enough to be hospitalized.

Expand the level of Blue Shield coverage of x-ray examinations beyond the present limits of $15 under Plan A and $25 under Plan B.

Provide equivalent coverage for x-ray examinations and laboratory determinations undertaken on ambulatory patients in the physician's office, in the hospital outpatient department or in the hospital when the patient is admitted for diagnosis.

Blue Cross covers x-ray examinations and laboratory determinations performed on a hospitalized bed patient undergoing treatment. It also provides benefits for these services in the emergency ward of a hospital within twelve hours of an accident and in the outpatient department when surgery is involved. Subject to a maximum of $15 per illness or injury under Plan A and $25 under Plan B, Blue Shield covers x-ray examinations undertaken in conjunction with medical, surgical or obstetric services. In no case does Blue Shield duplicate Blue Cross coverage, and there are no Blue Shield benefits for laboratory determinations.

Out of the experience that Blue Cross and Blue Shield have derived from administering the coverage described above, it was possible to lay down certain principles that served as the basis for subsequent development of a diagnostic rider to the basic Blue Shield contract. These are as follows:

1. Certain x-ray examinations and laboratory determinations can be covered in full because they are related directly to an unpredictable event, an unpleasant experience, or both. People do not have accidents or undergo cystoscopies in order to get x-ray benefits nor do many people enjoy being in the hospital. For these reasons it is possible to provide "Full Credit" for x-ray examinations and laboratory determinations:

   a. That in the case of a hospitalized bed patient are related directly to a major surgical procedure or a major endoscopic procedure carried out during the same period of covered hospitalization.

   b. That in the case of a hospitalized bed patient with an established diagnosis are undertaken to reveal the progress of definitive medical treatment carried out during the same period of covered hospitalization.

   c. That in the case of a non-hospitalized patient are undertaken immediately following an accident to determine the extent of a resultant acute injury or that are undertaken subsequent to an accident to determine the current status of a recent fracture except that no credit in excess of $50.00 per member should be provided in connection with any one accident.

   d. That in the case of a non-hospitalized patient are undertaken to determine the relationship between fetus and pelvis during current pregnancy.

   e. That in the case of a non-hospitalized patient are undertaken in conjunction with a laryngoscopy, bronchoscopy, esophagoscopy, gastroscopy, cystoscopy, myelography, or a similar major diagnostic procedure.

   f. That in the case of a non-hospitalized patient are undertaken within 90 days following discharge from the hospital to determine the current status of the condition for which the member was treated while in the hospital except that no credit should be provided for more than two such examinations in connection with any single period of hospitalization.

2. X-ray examinations and laboratory determinations that are not related directly to an unpredictable event, an unpleasant experience, or both, may be subject to abuse by patient, physician, or both, and some form of partial payment by the patient must be required if such services are to be covered at all. For this reason all x-ray examinations and laboratory determinations not covered by "Full Credit" should be covered by "Partial Credit" as follows:

   a. For x-ray examinations undertaken during any period of not more than seven (7) consecutive days, the member should pay the greater of $15.00 or 25 per cent of the total amount derived from the applicable Blue Shield Schedule of Fees.

   b. For laboratory determinations undertaken during any period of not more than seven (7) consecutive days the member should pay the greater of $10.00 or 25 per cent of the total amount derived from the applicable Blue Shield Schedule of Fees.

3. Small claims do not impose financial hardship upon the patient. Furthermore they are expensive to handle. It costs just as much to process a $10.00 claim as it does to process a $300.00 claim. For these reasons small claims should be eliminated in the "Partial Credit" category where utilization is at the discretion of the physician, patient, or both, by requiring the member to pay not less than $15.00 for x-ray examinations and $10.00 for laboratory determinations undertaken during any seven-day period.

4. With any new program it is wise to establish maximum liabilities. It is felt that in the "Partial Credit" category $150.00 under Plan A and $225.00 under Plan B per member per calendar year for x-ray examinations, laboratory determinations, or both, would be ample and still protect Blue Cross and Blue Shield.

5. In order to discourage unwarranted increases in the cost of medical care, fee schedules should be utilized. For this reason, the Blue Shield Schedules of Fees should be employed.

6. The Blue Shield service benefit concept should apply to any x-ray examination or laboratory determination that involves the direct interpretation of a physician.

7. No benefits should be provided for x-ray examinations or laboratory determinations made in conjunction with periodic health examinations or unless the member has unequivocal signs or symptoms of disease or injury requiring such services. Companies that make routine periodic health examinations available to their executives or other employees should not be subsidized by Blue Cross and Blue Shield.

8. Merely because benefits are available, unqualified and unequipped physicians should not be permitted to extend the scope of their Blue Shield practice through the installation of expensive equipment that may be obtained readily on a rental or lease basis.

9. Specialists in radiology and pathology should not be permitted to refer patients to themselves.

For financial reasons the foregoing principles are currently embodied in a rider to the basic Blue Shield contract that became effective on September 1, 1955. However, by July 1, 1956, it is anticipated that proper allocation of liability will be made between Blue Shield and Blue Cross and that all the diagnostic benefits provided by the two corporations will be included in a single joint Blue Cross-Blue Shield certificate.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR AUGUST, 1955

RÉSUMÉ

Disease	Aug. 1955	Aug. 1954	Seven-Year Median
Chancroid	1	2	1
Chicken pox	154	121	163
Diphtheria	0	1	6
Dog bite	1217	1525	1238
Dysentery, bacillary	22	15	7
Encephalitis, infectious	3	3	3
German measles	49	74	74
Gonorrhea	201	181	258
Granuloma inguinale	0	0	0
Hepatitis, infectious	34	87	23*
Lymphogranuloma venereum	0	1	1
Malaria	4	2	1
Measles	135	708	317
Meningitis, meningococcal	5	3	3
Meningitis, Pfeiffer bacillus	1	2	2
Meningitis, pneumococcal	2	0	0
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	6	5	5
Mumps	216	455	342
Poliomyelitis	1727	234	109
Salmonellosis	51	33	12
Scarlet fever	51	80	35
Syphilis	165	135	156
Trichinosis	1	2	3
Tuberculosis, pulmonary	216	238	186
Tuberculosis, other forms	14	17	13
Typhoid fever	1	2	3
Undulant fever	0	1	1
Whooping cough	84	159	166

*Six-year median.

Comment

Diseases below the seven-year median were chicken pox, diphtheria, German measles, measles, mumps, scarlet fever, typhoid fever and whooping cough.

For only the second time in the history of this state, no cases of diphtheria were reported during the month of August.

In only one other year (1953) was only a single case of typhoid fever reported during the month of August. The highest figure for this month was 803 cases recorded in August, 1910.

The 84 cases of whooping cough reported constituted the lowest figure for this disease for the month of August in the State's history.

Diseases above the seven-year median were bacillary dysentery, infectious hepatitis, poliomyelitis and salmonellosis.

Although infectious hepatitis was above the seven-year median for August, it was at its lowest level since July, 1952.

During August poliomyelitis reached its highest figure for any month in the history of the State.

Geographic Distribution of Certain Diseases

The following diseases were reported from the communities named:

Dysentery, bacillary: Danvers, 1; Marblehead, 1; Northampton, 1; Springfield, 1; Tewksbury, 1; Waltham, 17; total, 22.

Encephalitis, infectious: Chicopee, 1; Mendon, 1; Needham, 1; total, 3.

Hepatitis, infectious: Belchertown, 1; Boston, 3; Brockton, 1; Brookline, 1; Concord, 1; Dover, 1; Easton, 1; Fall River, 1; Gardner, 2; Gloucester, 1; Haverhill, 2; Holyoke, 1; Lowell, 1; Marlboro, 1; Mashpee, 1; Medford, 1; Needham, 1; New Bedford, 1; Newton, 1; Pittsfield, 3; Saugus, 1; Somerville, 1; Springfield, 1; Waltham, 1; Warren, 1; West Springfield, 2; Westford, 1; total, 34.

Malaria: Boston, 1; Chelsea Naval Hospital, 2; Wellesley, 1; total, 4.

Meningitis, meningococcal: Hingham, 1; Malden, 1; Methuen, 1; New Bedford, 1; Woburn, 1; total, 5.

Meningitis, Pfeiffer bacillus: Worcester, 1.

Meningitis, pneumococcal: Marion, 1; Revere, 1; total, 2.

Meningitis, undetermined: Cambridge, 2; Haverhill, 1; Lowell, 1; Springfield, 1; Waltham, 1; total, 6.

Meningitis, *Escherichia coli:* Holden, 1.

Poliomyelitis: Abington, 4; Acton, 1; Acushnet, 1; Adams, 1; Agawam, 5; Amesbury, 2; Amherst, 2; Andover, 6; Arlington, 12; Athol, 13; Attleboro, 7; Auburn, 2; Avon, 2; Barnstable, 6; Barre, 2; Bedford Air Force Base, 3; Bedford, 7; Bellingham, 1; Belmont, 3; Beverly, 11; Blackstone, 2; Boston, 406; Bourne, 1; Braintree, 30; Bridgewater, 4; Brockton, 51; Brookline, 18; Burlington, 4; Cambridge, 21; Canton, 5; Charlton, 3; Chatham, 1; Chelmsford, 1; Chelsea Naval Hospital, 1; Chelsea, 13; Chicopee, 8; Clinton, 5; Cohasset, 9; Concord, 6; Danvers, 9; Dedham, 11; Deerfield, 3; Dennis, 1; Dighton, 1; Dover, 1; Dracut, 4; Duxbury, 4; East Bridgewater, 3; East Brookfield, 1; Easthampton, 1; East Longmeadow, 2; Easton, 12; Essex, 1; Everett, 7; Fairhaven, 8; Fall River, 12; Falmouth, 6; Fitchburg, 9; Fort Devens, 2; Foxboro, 6; Framingham, 20; Franklin, 3; Gardner, 4; Gloucester, 4; Great Barrington, 2; Greenfield, 2; Groton, 1; Hadley, 1; Hamilton, 3; Hancock, 1; Hanover, 6; Hanson, 2; Harwich, 1; Haverhill, 4; Hatfield, 1; Hingham, 10; Holbrook, 10; Holliston, 2; Holyoke, 1; Hopedale, 7; Hudson, 14; Hull, 13; Ipswich, 3; Kingston, 2; Lawrence, 8; Lee, 3; Leicester, 3; Lenox, 4; Leominster, 6; Lexington, 7; Littleton, 2; Lowell, 3; Lunenburg, 3; Lynn, 28; Lynnfield, 4; Malden, 10; Manchester, 2; Mansfield, 3; Marblehead, 4; Marion, 4; Marlboro, 6; Marshfield, 10; Medford, 18; Medway, 3; Melrose, 8; Mendon, 1; Methuen, 3; Middleboro, 13; Milford, 13; Millis, 1; Milton, 4; Montague, 1; Mount Washington, 1; Natick, 14; Needham, 31; New Bedford, 16; Newburyport, 1; Newton, 50; Norfolk, 1; Northampton, 9; North Attleboro, 6; Northboro, 3; Northbridge, 2; North Reading, 2; Norton, 3; Norwood, 11; Orleans, 3; Oxford, 1; Palmer, 1; Peabody, 15; Pembroke, 4; Petersham, 1; Pittsfield, 8; Plainville, 1; Plymouth, 21; Plymptom, 1; Quincy, 87; Randolph, 9; Raynham, 3; Reading, 5; Rehoboth, 3; Revere, 14; Rockland, 5; Salem, 12; Sandwich, 2; Saugus, 4; Scituate, 11; Sharon, 3; Shrewsbury, 2; Somerset, 3; Somerville, 18; Southboro, 2; Southbridge, 4; South Hadley, 6; Southwick, 1; Springfield, 11; Sterling, 1; Stoneham, 3; Stoughton, 9; Swampscott, 2; Taunton, 11; Templeton, 1; Tewksbury, 4; Townsend, 1; Tyngsboro, 3; Upton, 2; Wakefield, 10; Walpole, 14; Waltham, 13; Wareham, 2; Watertown, 15; Wayland, 14; Wellesley, 11; Wenham, 2; Westboro, 1; West Bridgewater, 1; Westfield, 3; Westport, 1; West Springfield, 3; Westwood, 11; Weymouth, 47; Whitman, 1; Wilbraham, 1; Williamstown, 2; Wilmington, 1; Winchester, 3; Winthrop, 18; Woburn, 7; Worcester, 16; Wrentham, 3; Yarmouth, 3; total, 1727.

Salmonellosis: Agawam, 1; Barnstable, 1; Boston, 8; Brockton, 1; Brookline, 2; Burlington, 1; Cambridge, 2; Chicopee, 1; Fitchburg, 1; Haverhill, 3; Hopkinton, 1; Malden, 2; Needham, 1; Newton, 5; Rockport, 1; Somerville, 1; Springfield, 1; Waltham, 3; Watertown, 8; Wellesley, 1; Westfield, 1; Worcester, 5; total, 51.

Tetanus: Boston, 1; Chicopee, 1; Randolph, 1; total, 3.

Trichinosis: East Longmeadow, 1.

Tularemia: Chilmark, 1.

Typhoid fever: Springfield, 1.

BOOK REVIEWS

When Minds Go Wrong. By John M. Grimes, M.D. 8°, cloth, 246 pp., with frontispiece. New York: Devin-Adair Company, 1954. $3.50.

Since 1900 the general public has become greatly interested in the subject of mental illness. This is a very healthy sign because in the past ignorance concerning the facts about mental illness has been an obstacle to treatment and progress.

This special book, written by a man who has personally made careful investigation of public and private mental hospitals throughout the United States, attempts, with an almost missionary zeal, to find facts and put them in the author's own words into print for all to read. The book is particularly interesting to the degree that it reports his findings about the mentally ill and their care in mental hospitals. It is a poignant book, not written in the spirit of Pollyanna, but more with the point of view of Hogarth or Dickens, who first saw and documented Bedlam. There are some unpleasant facts in this book, but Dr. Grimes presents them in such a way that they may prove a spur to correction and better understanding of the many situations in state and private mental hospitals that need to be remedied. He deals particularly with the principles and the performance that he has observed. He also mentions the "pretentions," which come close to the legend of the Emperor's clothes. The most valuable chapter deals with the problems now pressing on the care of the mentally ill. This involves politics, medicine, law, public information, finance and the crucial problems of overcrowding, adequate personnel and good organization. One cannot put down this book with an easy heart. Properly interpreted, it may do much to help advance the cause of mental health in practical ways. The book ends with an extremely interesting chapter called "Prediction." It discusses the state hospital of tomorrow. Psychiatrists and physicians, as well as anyone interested in mental health, would do well to read Dr. Grimes's "Prediction."

MERRILL MOORE, M.D.

Chirurgie rozštěpů rtu a patra. **By Prof. Dr. František Burian. 8°, cloth, 302 pp., with 364 illustrations. Praha: Státní Zdravotnické Nakladatelstvi. Vázaný výtisk Kčs 69,-**

This monograph is written by a European surgeon eminent in the field of cleft palate and harelip. Though concise, it embodies the more important and progressive points of interest to all devoted to this field of medicine. In his introduction the author emphasizes the social problems posed by the increasing number of cases of cleft palate and harelip and encourages research into the preventive aspects of this subject.

The different types of clefts are demonstrated in a large series of photographs, and two main genetically different groups are identified.

In discussing the pathological anatomy and physiology of the parts affected, the author concludes that clefts do not represent a simple failure of fusion of embryonic facial processes but that there is a defect of tissue on both sides of the cleft as well as a reduced growth potential. He agrees with other authors on the subject regarding the inadequacy of the mesoderm as the basic cause of clefts in a chapter on etiology and suggests an international investigation into etiology that might eventually result in adequate preventive measures.

A special chapter discusses the secondary deformities of the upper jaw and alveolar processes as well as the influences responsible, the two most important of which are the actual deficiency of tissue and the reduced capacity of growth, possibly due to surgical trauma.

The "collective" treatment of cleft palate is urged — that is, the surgeon, the pediatrician, the stomatologist, the psychologist and the speech therapist should all work together, a view that has already become recognized in this country.

The author's operative procedures do not radically differ from those generally accepted by cleft-palate surgeons in this country. He operates on the average patient with cleft palate at about two years of age but advises postponement in the more extensive cases until the age of five years.

Since the publication of Victor Veau's book on cleft palate and cleft lips in 1930 the work on this subject by Dr. Burian is a very important contribution from European colleagues. Unfortunately, it is published in the Czechoslovakian language, with which few people are acquainted. It is a book that should be translated into English so that more English-speaking people can read it.

V. H. KAZANJIAN, M.D.

Progress in Allergy. Vol. 4. Edited by Paul Kallós, Helsingborg. 8°, cloth, 520 pp., with illustrations and tables. Boston: Little, Brown and Company, 1955. $20.00.

The fourth volume of *Progress in Allergy* possesses the same faults and virtues of its three predecessors. With the use of Taliaferro's table of connective-tissue cells involved in immune reactions, Dr. Kallós discusses the broad basis of such reactions and their relation to allergy. Dr. Bohrod writes a learned paper on the histology of allergic and related lesions. R. L. Mayer describes group sensitization to compounds of quinone structures. Raffel gives a detailed analysis of delayed hypersensitivities. The biosynthesis of adrenal steroids is delineated by Pincus, and the functional inter-relations between the anterior pituitary gland and the adrenal cortex by Engel. Dougherty postulates the mechanisms of action of adrenocortical hormones in allergy. Respiratory-tract allergy to fungous spores is described in full by Maunsell.

Each of these papers is undoubtedly erudite. The bibliographies are complete. Except, however, for occasional flashes of insight in the papers by Bohrod, Engel, Mayer and Pincus, most of the articles are, in truth, rather dull, giving the impression of having been written by experts who know "more and more about less and less." None of the papers are in any sense integrated with the others. The expert in each field will learn little that is new. For the nonexpert, there is more here than he is likely to want to know. As a reference book, this volume might find occasional use. It does not, however, represent "progress in allergy," and what it represents is certainly overpriced.

ETHAN ALLEN BROWN, M.D.

NONCLINICAL NOTES

MASSACHUSETTS TRUDEAU SOCIETY

At a meeting of the Massachusetts Trudeau Society the following officers were elected for 1955-1956: president, Dr. Edward J. Welch; vice-president, Dr. Norman J. Wilson; secretary-treasurer, Dr. Kenneth T. Bird.

NOTICES

NEW ENGLAND PEDIATRIC SOCIETY

A meeting of the New England Pediatric Society will be held in the auditorium of the Jimmy Fund Building, 35 Binney Street, Boston, on Wednesday, October 26. There will be a clinicopathological conference during the morning, and a scientific session in the afternoon. The evening speaker will be Dr. Wilburt C. Davison, who will talk on "Comparison of Child Care by American and British Methods."

MASSACHUSETTS HEART ASSOCIATION

A series of meetings to be known as "Stump the Cardiologist" will be offered by the Massachusetts Heart Association during the academic year 1955-1956.

At each meeting the cardiologist will define briefly some area of cardiology and invite the audience to submit written, unsigned questions for him to answer. He will be assisted by two general-practice physicians serving as moderators.

The six meetings will be held at 8:00 p.m. in the Jimmy Fund Auditorium, 35 Binney Street, Boston. The program is as follows:

October 19, 1955. Management and Prevention of Coronary Heart Disease. Dr. Paul D. White.

December 7, 1955. New Treatment of Arrhythmias. Dr. Samuel A. Levine.

January 25, 1956. Hypertension. Dr. Robert W. Wilkins.

February 29, 1956. Management of Congestive Failure. Dr. Howard B. Sprague.

March 21 and April 25, 1956. Open — to be nominated by the audience.

AMERICAN SOCIETY OF TROPICAL MEDICINE AND HYGIENE

There will be a meeting of the American Society of Tropical Medicine and Hygiene at the Hotel Somerset, Boston, November 2-5, 1955.

Further information may be obtained from Dr. Donald L. Augustine, Harvard School of Public Health.

YALE MEDICAL SOCIETY

A meeting of the Yale Medical Society will be held in Fitkin Amphitheatre at the Yale-New Haven Medical Center, New Haven, Connecticut, on Monday, October 10, at 8:15 p.m.

The speaker for the evening will be Dr. Charles Gardner Child, III. His subject will be "The Surgical Physiology of Portal Hypertension."

MEDICAL PERSONNEL VACANCIES

The Military District of Washington has announced vacancies for civilian medical officers for service in the Washington, D. C., area in the fields of general medicine, surgery, psychiatry, roentgenology and ophthalmology with the Department of the Army. Classified Civil Service status is not required. The salaries range from $8,645 to $10,065 a year. Further information may be obtained from the Civilian Personnel Office, Military District of Washington, Room 1543, Building T-7, Gravelly Point, Virginia (Washington, D. C.).

SOCIETY MEETINGS AND CONFERENCES

October 7, 1955–May 2, 1956. Postgraduate Medical Institute. Page 487, issue of September 15.

October 7 and 8. Academy of Psychosomatic Medicine. Page 509, issue of March 24.

October 7–27. Consultation Clinics for Crippled Children. Page 575, issue of September 29.

October 10. Yale Medical Society. Notice above.

October 10, 17 and 24, November 7 and December 5, 1955 and January 16, February 6, March 5 and April 2, 1956. Fried Lecture Series. Page 535, issue of September 22.

October 10–21. New York Academy of Medicine. Graduate Fortnight. Page 84, issue of July 14.

October 11, 18, 25 and November 1. Boston City Hospital House Officers' Association. Page 577, issue of September 29.

October 19. Massachusetts Society of Examining Physicians. Page 487, issue of September 15.

October 19 and December 7, 1955 and January 25, February 29, March 21, and April 25, 1956. Massachusetts Heart Association. Page 623.

October 19 and December 14, 1955 and February 15, March 28 and April 18, 1956. Greater Boston Medical Society. Page 203, issue of August 4.

October 20. Connecticut Academy of General Practice. Page 440, issue of September 8.

October 22. International Academy of Proctology. Page 487, issue of September 15.

October 22–26. American Heart Association. Scientific Session. Page 603, issue of April 7.

October 23–27. American Institute of Dental Medicine. Page 414, issue of March 10.

October 24-29. American College of Gastroenterology. Page 448, issue of September 15.

October 26. New England Pediatric Society. Page 623.

October 26 and November 30, 1955 and January 25, March 21 and April 26, 1956. Phi Delta Epsilon Fraternity Graduate Club Program. Page 118, issue of July 21.

October 27 and 28. New York Medical Conference. Page 394, issue of September 1.

October 27–29. Congress of Neurological Surgeons. Page 208, issue of August 4.

November 1–3. Henry Ford Hospital Symposium on Enzymes. Page 920, issue of May 26.

November 2–5. American Society of Tropical Medicine and Hygiene. Notice above.

November 6–13. Second International Congress of Allergology. Page 157, issue of January 27.

November 7–9. Association of Military Surgeons of the United States. Page 118, issue of July 21.

November 10–12. American College of Cardiology. Page 394, issue of September 1.

November 11 and 12. Inter-Society Cytology Council. Page 1056, issue of June 16.

November 14 and 18. American Public Health Association. Page 578, issue of September 29.

November 14 and 25. Course in Laboratory Diagnosis of Tuberculosis. Page 1102, issue of June 23.

November 19–21. American Association of Blood Banks. 8th Annual Meeting. Palmer House, Chicago, Illinois.

November 27 and 28. American College of Chest Physicians. Page 578, issue of September 29.

November 28–December 2. Interim Session of the American Medical Association, Boston.

December 5–14, 1955 and January 30–February 8, March 19–28 and June 4–13, 1956. Army Medical Service Postgraduate Course. Page 84, issue of July 14.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, OCTOBER 13

THURSDAY, OCTOBER 13

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*11:15 a.m.–12:00 m. Thoracic Conference. Ventilatory Studies before and after Pulmonary Resection. Dr. Warren J. Taylor. Main Amphitheater, Peter Bent Brigham Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.
5:00 p.m. Case Presentation and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Auditorium, New England Deaconess Hospital.

FRIDAY, OCTOBER 14

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Dr. Proger and staff. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–6:00 p.m. X-Ray Conference. Dr. Merrill Sosman. Stearns Auditorium, New England Center Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*7:30–9:30 p.m. Postgraduate Medical Institute. Cancer of the Stomach and Colon. Drs. Anglem and Gephart. Holyoke Soldiers' Home, Holyoke.

SATURDAY, OCTOBER 15

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Anesthesia Conference. Dr. Etsten and staff. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*9:00–10:30 a.m. Surgical Grand Rounds. Dr. Thibodeau and staff. Stearns Auditorium, New England Center Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*10:30 a.m.–12:00 m. Surgical History Meeting. Stearns Auditorium, New England Center Hospital.
*11:00 a.m.–12:00 m. Hematology Clinic. Dr. William Dameshek. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

MONDAY, OCTOBER 17

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Pediatric Medical-Surgical Rounds. Drs. Baty and Swenson. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Metabolism Conference. Dr. Schwartz. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.

(Concluded on page xxxiv)

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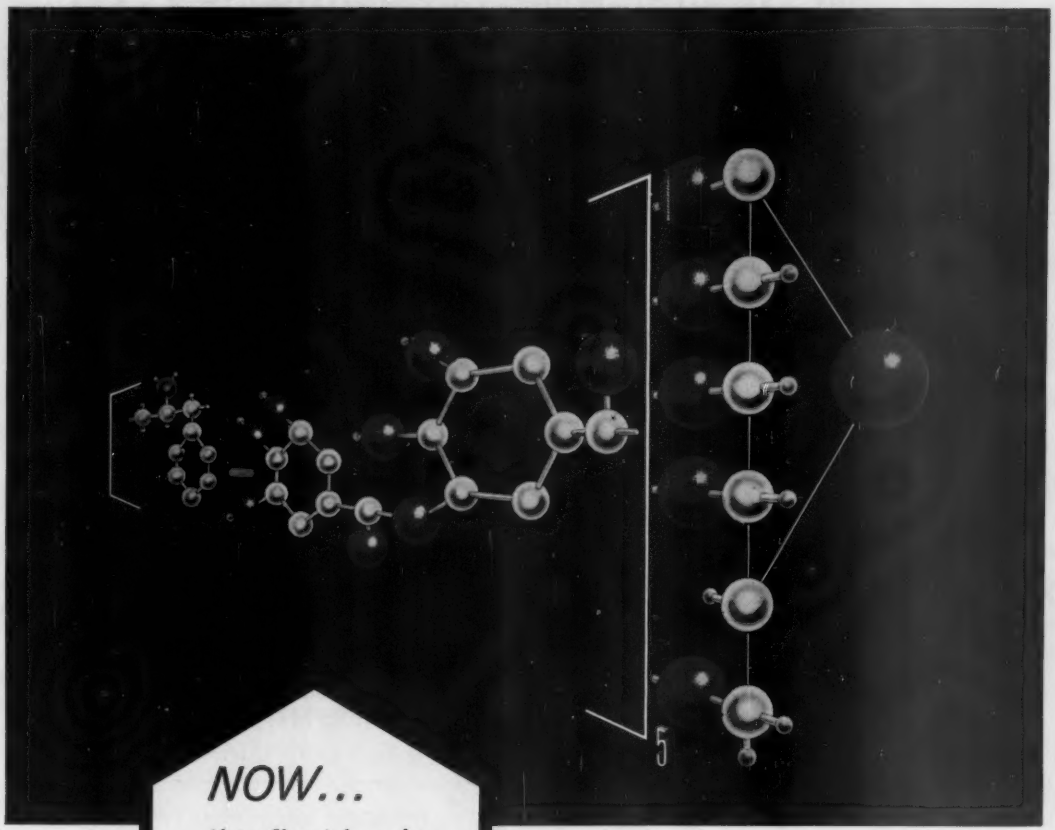

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Latest data on effectiveness of Furadantin

Flippin, H. F., and Eisenberg, G. M.: Antimicrobial Therapy in Medical Practice, Philadelphia, F. A. Davis Co., 1955, p. 40.

Clinical studies have demonstrated rapid clinical response in cases of cystitis and pyelonephritis, including infections caused by refractory organisms.

Trafton, H. M., et al.: New England J. Med. **252:** 383, 1955.

13 acute cases . . . 6 appeared cured . . . 6 markedly improved with no relapses.

36 chronic infections: 30 showed symptomatic improvement, frequently within 24 hours.

Beutner, E. H., et al.: Antibiotics Annual, 1954-1955, New York, Medical Encyclopedia, Inc., 1955, p. 988.

30 chronic urinary tract infections: Of 47 strains of bacteria isolated from these patients, 29 strains (62%) were eradicated by Furadantin.

Hasen, H. B., and Moore, T. D.: J.A.M.A. **155:** 1470, 1954.

Of patients with acute urinary tract infections, 95.7% were benefited. Patients with chronic infections and those with organic or obstructive lesions were benefited in 82% of cases.

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REFERENCES:

1. Blanchard, K. and Ford, R. A., Effective Antitussive Agent in the Treatment of Cough in Childhood, Journal-Lancet, 74:443, Nov., 1954.* **2.** Cass, L. J. and Frederik, W., Comparative Clinical Effectiveness of Cough Medication, Amer. Pract. and Dig. of Treat., Vol. 2, p. 844, October, 1951.*

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Also indicated in post-radiation sickness, nausea following surgery, Ménière's syndrome.

1. Weinberg, Arthur and Werner, W. E. F.: Bonadoxin, a new effective oral therapy for hyperemesis gravidarum. Am. Pract. and Dig. of Treatment. In press. 2. Personal communication. 3. Berenson, F.: Bonadoxin: oral therapy for nausea and vomiting of pregnancy. In press.

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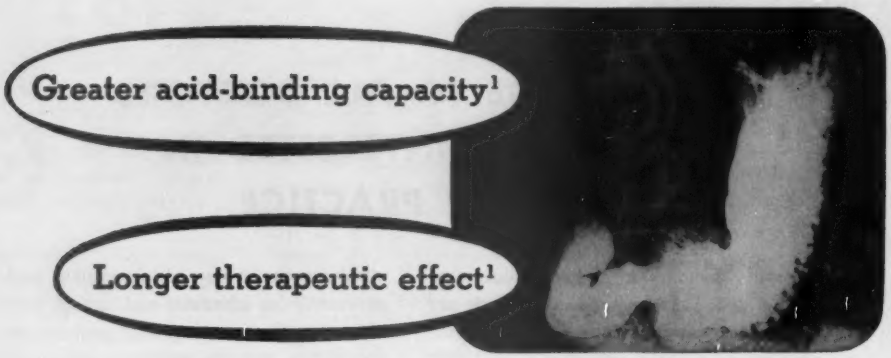

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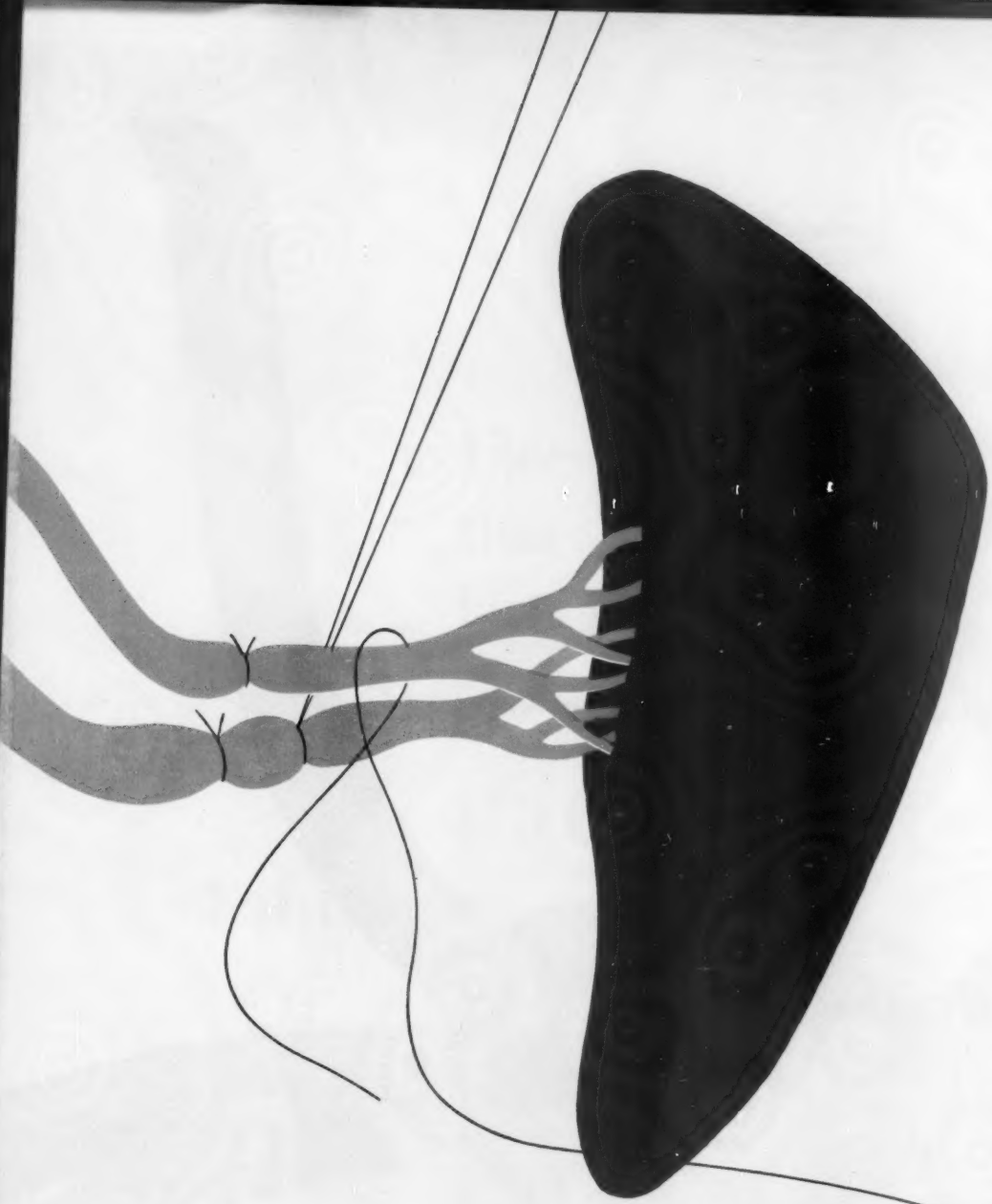

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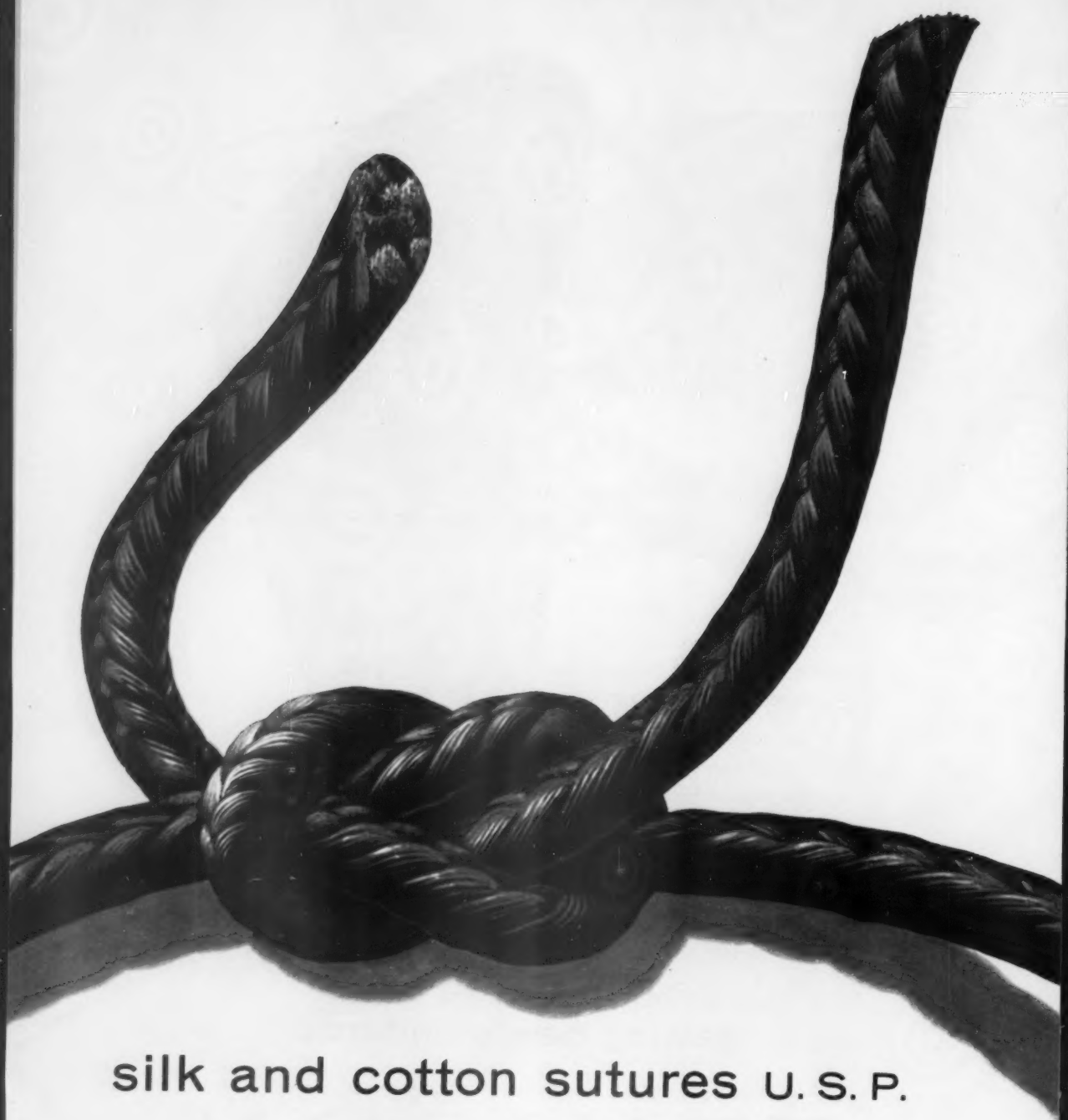

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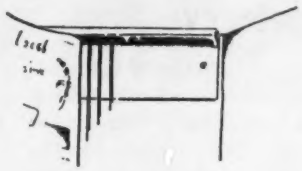

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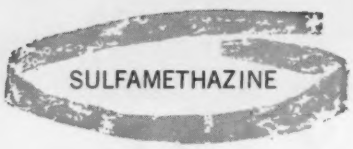

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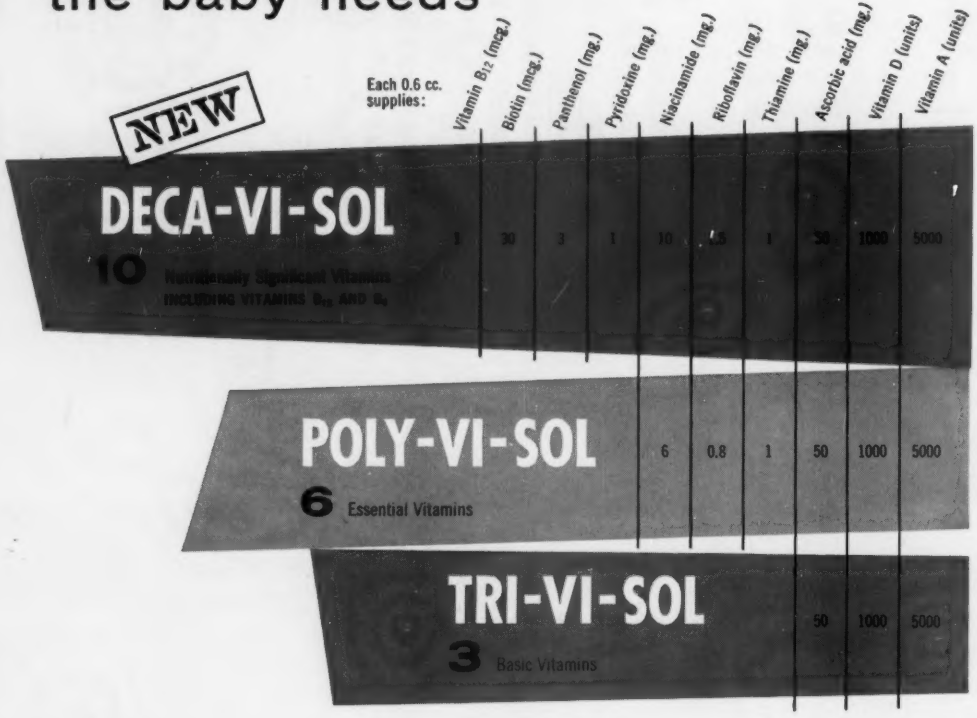

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